THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

AUGUST, 1958

ORIGINAL ARTICLES

SERUM TRANSAMINASE VALUES AFTER CHOLECYSTECTOMY, HYSTERECTOMY, AND OPERATIONS ON THE FRACTURED HIP

By Albert A. Fisk, M.D.

Robert G. Thomas, M.D.

and

Jonas Maurukas, Ph.D.

Elyria, Ohio

The serum glutamic oxaloacetic transaminase has become a widely used test in the diagnosis of acute myocardial infarction. Its accuracy is stated to be over 95% (Conrad[2]). High levels have been reported, however, in hepatocellular disease (Mason and Wroblewski[5], and Wroblewski and LaDue[9]), pulmonary infarction (Denny *et al.*[3] and Mason and Wroblewski[5]), acute pancreatitis (Chinsky, Shmagranoff and Sherry[1]) embolism of the leg (Merrill *et al.*[6]), and gangrene (Chinsky, Shmagranoff and Sherry[1]), so that the usefulness of the serum transaminase in the diagnosis of myocardial infarction is tempered by the realization that it is a nonspecific test. Moreover, any infarcted tissue seems to cause a rise in the serum transaminase since Rudolph *et al.*[8] found that ligation of the renal, splenic, mesenteric, or pulmonary artery in dogs consistently gave elevated serum transaminase values.

Recently at the Elyria Memorial Hospital there was a patient who had had a cholecystectomy in whom the diagnosis of myocardial infarction was suspected. Clinical evaluation and electrocardiograms were not diagnostic, but the serum transaminase value was elevated. A review of the literature at that time did not reveal any information on the effect of surgical procedures on the level of this enzyme. Since the internist is frequently asked, after an operation, to evaluate a patient for possible myocardial infarction, and since electrocardiograms and clinical evaluation are not always clear-cut diagnostically in this type of patient, a study of serum transaminase values in certain patients after operation was undertaken.

Method. Serum glutamic oxaloacetic transaminase values were determined according to the method of Karmen[4]. Normal values are 5 to 40 units per ml. serum. Patients were selected at random from the wards of the Elyria Memorial Hospital. Pre-operatively a serum transaminase, a base line electrocardiogram and a liver function test were done. After operation serum transaminases were done at 12, 24 and 48 hours. Patients

were evaluated clinically pre- and postoperatively, and if elevated serum transaminase levels occurred postoperatively, the electrocardiogram and liver function tests were repeated. In no case was there reason to believe that a myocardial infarction had occurred after operation.

Results. The results are summarized in Tables 1, 2 and 3. It is readily seen that 9 of 10 patients with biliary tract operations showed a postoperative rise in the serum transaminase of over 40 units. The median highest value was between 55 and 81 units, and 4 of 9 highest values were over 100 units, one rising to 340 units. Usually the highest value was recorded at 12 hours after operation; values were frequently elevated at 24 hours; and only one value was over 40 units at 48 hours. The rise was, therefore, transitory and seems unlikely to be related to hepatocellular dysfunction, since elevations of the serum transaminase then usually persist for many days. This conclusion is further borne out by the infrequent occurrence of abnormal liver function tests postoperatively (Table 1). Six of 10 patients had common duct explorations, but only 3 of these had elevations above the median value; hence common duct exploration did not seem to be a significant factor in elevating values. The presence or absence of postoperative complications and the relative degree of inflammation and edema at the time of surgery seemed to bear little relation to the extent of the rise.

Ten patients who had had hysterectomies, both abdominal and vaginal, showed normal serum transaminase values throughout the 48-hour period studied. In operations for intertrochanteric hip fractures 2 of 11 patients showed a serum transaminase rise of over 40 units after operation. In one of these patients, it is felt operative trauma may have played a significant part in the rise.

Discussion. It is apparent from our study that the level of the serum transaminase after surgery depends on the particular procedure involved. After cholecystectomy the serum transaminase, as an aid in the diagnosis of myocardial infarction, is useless. Also after operations on the hip, serum transaminase elevations would have to be interpreted with caution. Following hysterectomy, however, a rise in serum transaminase would seem to be a valid diagnostic aid. Values after other procedures require further study, if this test is to be interpreted correctly.

The reason for the rise after biliary tract surgery is not clear. It does not seem to be related to trauma, hepatocellular dysfunction, common duct exploration, or pre-operative obstructive jaundice. Bile is stated to contain large amounts of the enzyme, 2000 units per ml., and it may be that handling of the biliary tract results in some increased absorption of the enzyme into the vascular system.

Recently, Nickell and Allbritten[7] reported on serum transaminase values in a group of patients after operation. In patients after 25 of 81 various surgical operations they found elevations of over 40 units. Although they felt operative trauma played a part, they noted in 5 of 8 biliary tract operations, 8 of 14 cardiovascular procedures, and 3 of 4 amputations the patients had elevated serum transaminase values, whereas only 2 of 17 patients after other abdominal operations and none of 7 orthopedic operations had elevations. Our results are of a similar nature, emphasizing the high serum transaminase value after biliary tract surgery.

Summary. 1. Serum transaminase values at 12, 24 and 48 hours after cholecystectomy, hysterectomy and operations on the fractured hip are recorded.

TABLE 1.—CHOLECYSTECTOMY

TABLE 1.—CHOLECYSTECTOMY

		PRE-OPERATIVE		POSTOPERATIVE							
				SERUM TRANSAMINASE							
PT	OPERATION	ECG	T.T.	0 hrs.	12 hrs.	24 hrs.	48 hrs.	ECG	BSP‡	T.T.*	REMARKS
A.H.	Cholecystectomy	T wave changes		21	81	45	55	Same	5%	2	Common duct exp. Benign postop.
T.P.	"	Normal		21	45	27	26	Same	5%	2	Pericholecystic abscess
E.G.	"	T wave changes		37		55	37	Same	5%	3	Common duct exp. Postop. Pneumonia
F.H.	"	Normal	C.F.† neg.	8	102	59	27	T wave changes	55%	C.F. neg	Common duct exp. Liver biop.—cirrhosis
V.J.	"	Normal	C.F. neg.	6	340	128		normal	7%	C.F. neg.	Benign postop. Active peptic ulcer
A.S.	"	Normal	C.F. neg.	4	46	46	20	normal	0%	C.F. neg.	Benign postop.
S.N.	"	Normal	6	26	104	55	30	T wave change	15%	5	Weak postop.
B.F.	"	Normal	2	14	54	40	24	normal	0%	2	Common duct exp. Benign postop.
C.H.	"	Normal	2	50	101	75	28	normal			Common duct exp. Ob. Jaundice.
G.S.	"	L.V.H.	1	40	20	16	12				Common duct exp. Ob. Jaundice

* Thymol turbidity units
† Cephalin flocculation
‡ Bromsulphalein retention at 45 min.

TABLE 2.—HYSTERECTOMY

		PRE-OPERATIVE		POSTOPERATIVE							
				SERUM TRANSAMINASE							
PT	OPERATION	ECG	T.T.	0 hrs.	12 hrs.	24 hrs.	48 hrs.	ECG	BSP	T.T.	REMARKS
R.T.	Abdominal Hysterectomy	Normal		26	21	16	20				C. Section; Diabetic
K.L.	Vaginal Hysterectomy	Normal	4	12	16	15	13				
V.L.	Abdominal Hysterectomy	Normal	3	25	22	26	15				
M.P.	Vaginal Hysterectomy	T wave changes	4	10	24	24	29				
R.D.	Abdominal Hysterectomy	Normal	5	13		7	10				
A.C.	"	T wave changes	3	15	12	16	30				
A.E.	"	Normal	2	11	16	14	17				Urinary tract Inf.
R.A.	Vaginal Hysterectomy	Normal	10	13	10	9	13				
R.O.	Abdominal Hysterectomy	Normal	4	15	16	16	11				Carcinoma cervix Previous x-ray Rx
D.C.	Abdominal Hysterectomy	Normal	4	15	15	14	9				

TABLE 3.—FRACTURED HIP

		PRE-OPERATIVE		POSTOPERATIVE							
				SERUM TRANSAMINASE							
PT	*OPERATION*	*ECG*	*T.T.*	*0 hrs.*	*12 hrs.*	*24 hrs.*	*48 hrs.*	*ECG*	*BSP*	*T.T.*	*REMARKS*
K.B.	Eichler Pro.	L.V.H.	3		78	120	94		3%	3	Hip dislocated
J.L.	S. P. nail	Normal	12	15	27	25	25				Postop. pneumonia
M.S.	"	Normal	5	7		16	16				
J.B.	"	St changes	4	8	11	9	7				
K.D.	Jones Arthr.	Normal	1	13	10	13	18				
E.H.	S. P. nail	Normal	1	19	28	30	37				Parkinsonism
A.P.	"	L.V.H.	6	11	12	16	9				
B.W.	"	T wave changes	3	15	18	5	17				Postop. pul. embolus
J.C.	"	L.B.B.B.	3	17	27	39	54				Postop. pneumonia
H.H.	"	Normal	2	12	19	27	28				Postop. weakness
E.S.	"		5	12	13	13					

2. Serum transaminase values are elevated in patients after cholecystectomy, and the test is not then a valid index of myocardial infarction.

3. Elevations of the serum transaminase in patients after hysterectomy can be an aid in the diagnosis of myocardial infarction, but elevations after operations on the fractured hip must be interpreted with caution.

REFERENCES

1. **Chinsky, M., Shmagranoff, G. L.,** and **Sherry, S.:** J. Lab. & Clin. Med., **47,** 108, 1956.
2. **Conrad, F. G.:** New England J. Med., **256,** 602, 1957.
3. **Denny, J. L., McAuley, C. B., Martin, H. E., Ware, A. G.,** and **Segalove, M.:** J. Am. Med. Assn., **161,** 614, 1956.
4. **Karmen, A. J., Wroblewski, F.,** and **LaDue, J. S.:** J. Clin. Invest., **34,** 126, 1955.
5. **Mason, J. H.,** and **Wroblewski, F.:** A.M.A. Arch. Int. Med., **99,** 245, 1957.
6. **Merrill, J. M., Lemley-Stone, J., Grace, T. J., Jr.,** and **Meneely, G. R.:** J. Am. Med. Assn., **160,** 1454, 1956.
7. **Nickell, W. K.,** and **Albritten, F. F., Jr.:** Surgery, **42,** 240, 1957.
8. **Rudolph, L. A., Schaefer, J. A., Dutton, R. E.,** and **Lyons, R. H.:** J. Lab. & Clin. Med., **49,** 31, 1957.
9. **Wroblewski, F.,** and **LaDue, J.:** J. Am. Med. Assn., **160,** 1130, 1956.

SUMMARIO IN INTERLINGUA

Valores De Transaminase Seral Post Cholecystectomia, Hysterectomia, E Operationes Pro Fracturas Coxal

1. Es registrate valores de transaminase seral a periodos de 12, 24, e 48 horas post cholecystectomia, hysterectomia, e operationes pro fracturas coxal.

2. Le valores de transaminase seral es elevate in patientes post-cholecystectomic. In tal casos le test non es valide como indice de infarcimento myocardial.

3. Elevationes del transaminase seral in patientes post-hysterectomic pote esser de adjuta in le diagnose de infarcimento myocardial. Elevationes post operationes pro fracturas coxal, del altere latere, debe esser interpretate cautissimemente.

THE CALCIUM-DIGITALIS TOLERANCE TEST: A BRIEF RÉSUMÉ WITH DERIVATION OF CLINICALLY USEFUL FORMULAE*

By Gerald C. Timmis, M.D.
RESIDENT IN INTERNAL MEDICINE, HARPER HOSPITAL

Robert M. Nalbandian, M.D.
FELLOW IN PATHOLOGY, DEPARTMENTS OF PATHOLOGY,
WAYNE STATE UNIVERSITY COLLEGE OF MEDICINE AND DETROIT RECEIVING HOSPITAL

Seymour Gordon, M.D.
RESIDENT IN INTERNAL MEDICINE, HARPER HOSPITAL

AND

Robert J. Schneck, M.D.
CLINICAL PROFESSOR OF MEDICINE, WAYNE STATE UNIVERSITY COLLEGE OF MEDICINE;
CHIEF, DEPARTMENT OF INTERNAL MEDICINE, HARPER HOSPITAL
DETROIT, MICHIGAN

The recently proposed Calcium-Digitalis Tolerance Test (Nalbandian *et al.*[5-7]) is a quantitative, clinical technique whereby the existing level of digitalization present in a patient may be determined. By the use of formulae, maximum safe complemental doses of digitalis may be calculated and administered if therapeutically indicated. This paper discusses the derivation of these formulae after a brief review of the principle and clinical data of this test.

The determination of the level of digitalization by this test has been made in terms of the patient's individual total tolerance for digitalis measured to the threshold of toxicity. The existing level of digitalization can then be expressed as a percentage of tolerance or toxicity. From such quantitative data and by use of the formulae below, precise, maximum, safe complemental doses of digitalis have been calculated and administered. This test has been performed 24 times in 15 adult patients in congestive failure and calculated complemental doses have been administered; all without complication or mortality. The details of the technique of the test and the summary of the complete clinical data have been recorded (Nalbandian, Gordon and Kaufman[7]).

The principle of this test is based upon the similarity of action on the myocardium between calcium and digitalis and upon the inverse, quantitative synergistic relationship between calcium and digitalis in reference to the production of electrocardiographic endpoints (EKG changes of digitalis toxicity). Essentially, the test is as follows: In a patient given digitalis to nontoxic levels a titration to an EKG endpoint is accomplished by progressive increments at regular intervals of intravenously administered 10% $CaCl_2$. Depending upon which dose in the prescribed dosage schedule of $CaCl_2$ provokes the EKG endpoint, a determination of the existing level of digitaliza-

*Supported by the Spaulding Fund of Harper Hospital.

For reprints please address: Robert M. Nalbandian, M.D., Department of Pathology, College of Medicine, Wayne State University, Detroit 7, Michigan.

tion is possible. This is true because of an inverse relationship which exists between levels of digitalization and the gradient of hypercalcemia required to produce EKG endpoints. So, the greater the individual myocardial sensitivity for digitalis or the higher the existing level of digitalization, or both, the sooner the EKG endpoints will be provoked by one of the earlier and smaller doses of $CaCl_2$. Thus, the level of digitalization can be expressed as a per cent of toxicity in terms of the individual total tolerance for the drug measured to the point of toxicity.

An important feature of this test, aside from the quantitative aspects, is the demonstrated fact (Nalbandian *et al.*[6,7]) that provoked EKG endpoints are under *immediate* and *complete* control by virtue of two mechanisms. One is the normal physiologic mechanism of a rapid serum calcium clearance rate (Bronner *et al.*[2]). This serum calcium clearance rate has been determined to be in part an inverse function of age, varying in greatest measure with the skeletal activity in capturing calcium (Bronner and Harris[1], Hansard, Comar and Davis[4] and Thomas *et al.*[11]). Thus the synergism supporting the EKG endpoint is quickly dissipated. If the EKG endpoint should persist or become emergent, the second available mechanism for aborting the EKG endpoint has proven unfailingly effective[5-7]. This is the intravenous use of Na_2EDTA* (Edethamil, Versene), a well-known calcium chelating agent which renders physiologically unavailable the stoichiometrically sequestered calcium. The EKG endpoint is thus effectively and immediately interrupted (Nalbandian *et al.*[5-7], Gubner and Kallman[3], Page and Real[8], Sapeika[9] and Smith and Grinnell[10]). In the clinical trials of this test[7] Na_2EDTA was required to control the EKG endpoints only 4 times in 24 trials. In the remaining 20 instances the EKG endpoint spontaneously reverted to normal patterns due, we feel, to the normal physiologic serum calcium clearance mechanism.

If enough calcium is given rapidly intravenously, EKG changes indistinguishable from digitalis intoxication are produced[6]. To have significance, therefore, the test dosage schedule of $CaCl_2$ must be of such an order, increment, concentration and interval that when the entire test dosage schedule has been administered intravenously in *nondigitalized* patients, EKG endpoints will *not be provoked*. But, when such a schedule of dosage is administered in digitalized patients, specific, recognizable EKG evidence of digitalis toxicity (EKG endpoints) will be produced.

The test dose schedule of 10% $CaCl_2$ already published[7] has been useful for the adult age group. Since the serum calcium clearance is an inverse function of age in great measure, it follows that for the extremes of age, new and separate test schedules will have to be developed which will accommodate the different rates of serum calcium clearance operative in each group. Precisely because the serum calcium clearance rates are greater in the pediatric age group, this test should find ideal application in that group. The $CaCl_2$ test dose schedules for the geriatric and pediatric age groups still remain to be published and are under investigation at present.†

*Prepared in pharmaceutical quality by Riker Laboratories, Los Angeles 54, California.

†In association with Dr. A. C. Nolke, Associate Chief of Pediatrics, Childrens' Hospital, Detroit, Michigan, a modification of the test dose schedule (increments of 3.3% $CaCl_2$) has been successfully adapted for use in a single infant in congestive failure. By the use of the Calcium-Digitalis Tolerance Test and by the use of the formulae, a maximum, safe, level of digitalis was computed and administered without encountering digitalis intoxication. Data upon request.

Discussion and Derivations. On the basis of data published elsewhere[5-7] it may be granted that in a digitalized patient submitted to the Calcium-Digitalis Tolerance Test, that a "percentage-of-toxicity" significance accrues to the particular EKG endpoint provoking dose of $CaCl_2$: Such that, for example, the EKG endpoints provoked by the fifth and eighth doses of 10% $CaCl_2$ this can be expressed:

$$(1) \qquad D_1 = (T)\, X_1$$

solving for the toxic dose (T):

$$(2) \qquad T = \frac{D_1}{X_1}$$

and from Fig. 1 it is evident that the toxic dose (T) less the digitalizing dose (D_1) is equal to a'. Then:

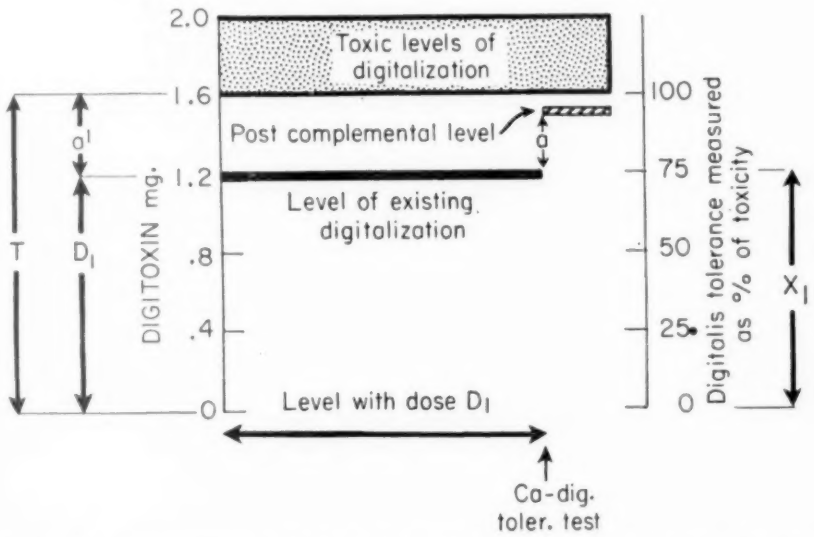


Fig. 1.—A schematic summary of the level of digitalization achieved in a patient who received a single digitalizing dose, D_1, and a complemental dose, a. T = toxic dose of digitoxin; D_1 = original digitalizing dose; a' = the complemental dose of digitoxin whereby the resulting level of digitalization will just attain threshold of toxicity; a = the corrected complemental dose of digitoxin which results in a level of digitalization short of toxicity; X_1 is a measure of the level of digitalization expressed as a per cent of total tolerance or toxicity. See text.

signify respectively that the patient has been digitalized to 50% and 75% of his total tolerance for a particular digitalis preparation. By simple algebra we can derive certain equations useful in the calculation of maximum safe complemental doses of digitalis.

From Fig. 1 it is clear that the "digitalizing dose" can be expressed as a percentage of the toxic dose. Thus, where

D_1 = original digitalizing dose
T = toxic dose
X_1 = % of toxicity as measured by the Calcium-Digitalis Tolerance Test

$$(3) \qquad \frac{D_1}{X_1} - D_1 = a'$$

$$(4) \qquad \frac{D_1 - D_1 X_1}{X_1} = a'$$

$$(5) \qquad \frac{D_1 (1 - X_1)}{X_1} = a'$$

But if the complemental dose, a', is given to the patient, the threshold of toxicity will just be reached. The extent to which a' will approach the toxic threshold can be controlled by introducing into (5) a constant, k, with a value of less than 1 (.8 for example):

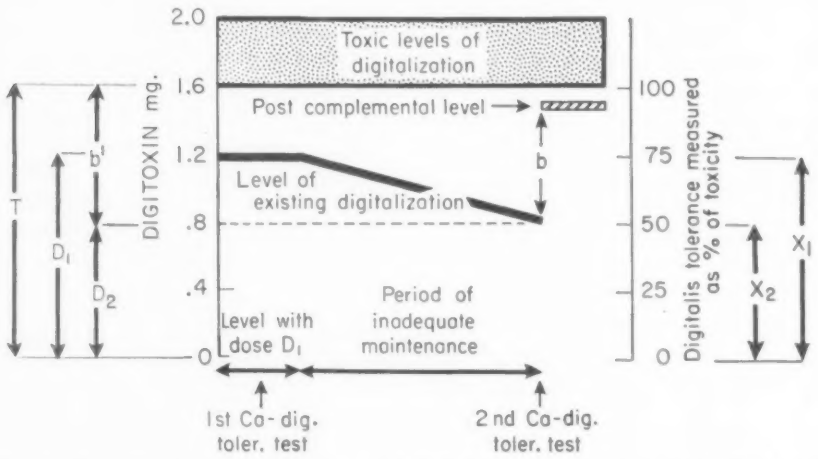


Fig. 2.—A schematic summary of the levels of digitalization in a patient originally digitalized with a dose (D_1) of digitoxin, inadequately maintained, and whose level of digitalization when measured in terms of tolerance fell from 75% (X_1%) to 50% (X_2%). T = toxic doses; D_1 = original dose of digitoxin; X_1 is the measure of the level of digitalization expressed as a per cent of total tolerance or toxicity resulting from dose D_1; X_2 is a similar measure of the level of digitalization present at the time of the second test; D_2 is unknown and can be regarded as that equivalent digitalizing dose which if given to the same patient in a nondigitalized state would result in a level of digitalization of X_2% of toxicity or total tolerance; b' = complemental dose which if given after the second test would render the patient just toxic; b = the corrected complemental dose of digitoxin which if given after the second test would result in a level of digitalization just short of toxicity. See text.

$$(6) \qquad k\left[\frac{D_1\,(1-X_1)}{X_1}\right]=a$$

Thus a is equal to the single, maximum, safe complemental dose of digitalis.

For example: A patient is digitalized with 1.2 mg. (D_1) of digitoxin. The level of digitalization by the test is determined to be 75% (X_1) of his total tolerance. Substituting in *(6)*

$$k\left[\frac{1.2\,(1-.75)}{.75}\right]=a$$

$$k\left[\frac{1.2\,(.25)}{.75}\right]=a$$

$$.8 \quad (.4)=a$$

$$.32=a$$

So a maximum of .32 mg. of digitoxin can safely be tolerated in addition to the "digitalizing dose."

In Fig. 2 there is schematically summarized an hypothetical case in which the patient was previously digitalized with a dose (D_1) of digitoxin and wherein the resulting level of digitalization attained was determined to be X_1% of his total tolerance. The patient then was placed on an inadequate maintenance dose of digitoxin and some weeks subsequently was tested a second time and the level of digitalization then had dropped to X_2% of his total tolerance. D_2 is unknown and can be regarded as that equivalent digitalizing dose which if given to the patient in a nondigitalized state would result in a level of digitalization of X_2% of his total tolerance. Then from Fig. 2 it is evident that:

$$(7) \qquad \frac{D_1}{D_2}=\frac{X_1}{X_2}$$

$$(8) \qquad D_2=\frac{D_1\,X_2}{X_1}$$

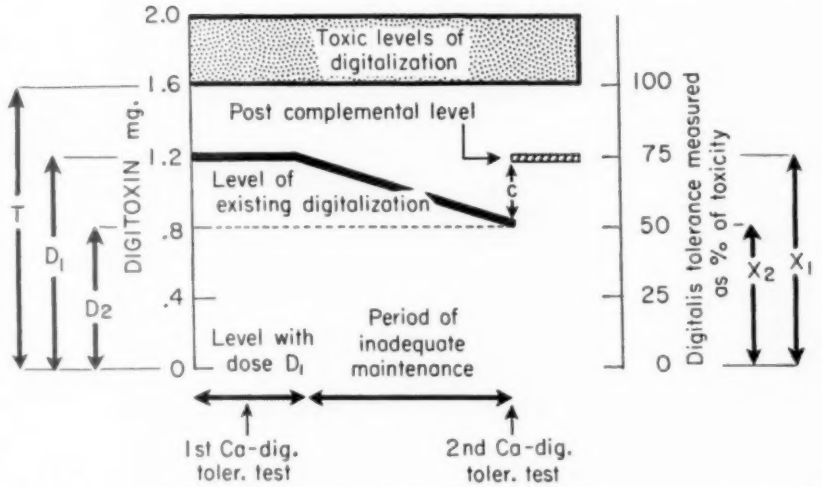


Fig. 3.—A schematic summary of the levels of digitalization in a patient originally digitalized with a dose (D_1) of digitoxin, inadequately maintained, and then restored by complemental dose, c, to levels achieved by the original digitalization. T = toxic dose; D_1 = original digitalizing dose; X_1 is the measure of the level of digitalization expressed as a per cent of total tolerance or toxicity resulting from dose D_1; X_2 is a similar measure of the level of digitalization present at the time of the second test; D_2 is unknown and can be regarded as that equivalent digitalizing dose which if given to the same patient in a nondigitalized state would result in a level of digitalization of X_2% of total tolerance or toxicity; c = the complemental dose of digitoxin which if given to the patient after the second test would restore the level of digitalization to that attained by the original dose (D_1) of digitoxin. See text.

And since in Fig. 2 the toxic dose (T) less the digitalizing dose (D_2) is equal to b′ and since from (2) $T = \frac{D_1}{X_1}$, we see that

$$(9) \qquad \frac{D_1}{X_1} - D_2 = b'$$

$$(10) \qquad \frac{D_1}{X_1} - \frac{D_1 X_2}{X_1} = b'$$

$$(11) \qquad \frac{D_1 (1-X_2)}{X_1} = b'$$

For the same reasons as above k is put into equation *(11)* and we have

$$(12) \qquad k\left[\frac{D_1 (1-X_2)}{X_1}\right] = b$$

From Fig. 2 it will be seen that b in expression *(12)* corrects the inadequate level of digitalization to maximum safe levels just short of the toxic threshold.

For example: Let us take the 1st example in which the patient received 1.2 mg. (D_1) of digitoxin and was digitalized thereby to a level of 75% (X_1). On inadequate maintenance dosage his level of digitalization dropped to 50% (X_2) of his total tolerance as detected by the second test weeks later. Substituting in *(12)*:

$$k\left[\frac{1.2\ (1-.50)}{.75}\right] = b$$

$$.8 \quad (.8) = b$$

$$.64 = b$$

Thus, after inadequate maintenance on digitoxin the maximum safe dosage of digitalis the patient can now receive is .64 mg. of digitoxin.

A third expression can be derived which, in the case of an inadequately maintained patient, will restore the level of digitalization to that achieved by the original digitalization. From the schematic summary in Fig. 3, the origi-

nal digitalizing dose (D_1) achieved a level of digitalization of X_1% of his tolerance. After an interval of inadequate maintenance the level of digitalization fell and was then determined by a second test to be X_2% of his tolerance. D_2 again can be regarded as that equivalent digitalizing dose which if given to the patient in a nondigitalized state would result in a level of digitalization of X_2% of his tolerance. Then from Fig. 3:

$$(13) \qquad \frac{D_1-D_2}{D_2} = \frac{X_1-X_2}{X_2}$$

$$(14) \qquad D_1 X_2 = D_2 X_1$$

$$(15) \qquad D_2 = \frac{D_1 X_2}{X_1}$$

Since in Fig. 3 the difference in dosage between D_1 and D_2 is equal to the complemental dose, c, we have:

$$(16) \qquad D_1-D_2=c$$

$$(17) \qquad D_1 - \frac{D_1 X_2}{X_1}=c$$

$$(18) \qquad \frac{D_1 X_1-D_1 X_2}{X_1}=c$$

$$(19) \qquad \frac{D_1 (X_1-X_2)}{X_1}=c$$

For example: Again from our first illustration, the original digitalizing dose was 1.2 mg. (D_1) of digitoxin and the corresponding level of digitalization achieved was 75% (X_1). After an interval of inadequate maintenance, the existing level of digitalization was determined by a second test to be 50% (X_2) of his tolerance. What is the dose of digitoxin which will restore the level of digitalization to that originally attained by D_1? Substituting in *(19)*:

$$\frac{1.2\ (.75-.50)}{.75}=c$$

$$.4=c$$

Therefore, .4 mg. will restore the level of digitalization to that achieved by the original digitalizing dose.

Conclusions and Comments. In these formulae the complemental dose of digitalis is calculated in terms of the same digitalis preparation as that used in the original digitalization. These formulae (Nos. 6, 12, and 19) can be adapted for the calculation of complemental doses of digitalis preparations of a potency per milligram differing from that used for the original digitalization (for example, Cedilanid or Digoxin complementing digitoxin). However, there will be required a unit which will interrelate precisely the various potencies in terms of a common unit. Cat units may be used for this purpose. But it will be found that calculations using Cat units will tend to be smaller than the maximum theoretical amount of the complemental dose due to inherent inaccuracies of Cat units themselves[7].

We believe that by means of this Calcium-Digitalis Tolerance Test and with the use of the formulae derived above it is now possible to achieve an order of precision in digitalis dosage not heretofore possible.

This test is *NOT* intended to be used in the usual cardiac failure requiring digitalis therapy. Rather its use should be reserved for that small group of cases of congestive failure in which the level of digitalization is of therapeutic importance and in real question. For example, this test has proven useful and accurate in resolving the clinical conundrum in which it is difficult to ascertain whether arrythmias of sudden onset in a digitalized patient are the result of (A) hypoxia and increased myocardial irritability due to decompensation and inadequate digitalization or (B) digitalis intoxication. The successful differentiation of this clinical problem in 3 cases by the use of the Calcium-Digitalis Tolerance Test is reported elsewhere[7].

On the basis of our experience with the Calcium-Digitalis Tolerance Test we venture to predict that pediatric problems in levels of digitalization

will be particularly susceptible to solution with its use. This is due in great measure to the more rapid serum calcium clearance rates obtaining in the pediatric age group.

Summary. 1. The literature, principles, experimental, and other data of the first 24 clinical trials of the Calcium-Digitalis Tolerance Test are very briefly summarized and pertinent references are cited.

2. The *effective* and *immediate* control of the EKG endpoints (signs of digitalis intoxication provoked by action of calcium and digitalis) by the use of intravenous Na_2EDTA is discussed. Confirmatory experimental work is cited.

3. Three clinically useful formulae (Nos. *6*, *12*, and *19*) are derived. In conjunction with quantitative data from the Calcium-Digitalis Tolerance Test hypothetical examples of the use of these formulae to calculate maximum, safe, complemental dosages of digitalis are offered.

4. The Calcium-Digitalis Tolerance Test is intended for use in the *uncommon* clinical problems of digitalization. It has been used successfully to differentiate, for example, whether arrythmias in cases of cardiac failure are the consequence of inadequate digitalization or digitalis intoxication. This test may be used also to digitalize a patient, when therapeutically indicated, to maximum, safe levels just short of digitalis intoxication.

5. The induced transient hypercalcemia incident to the performance of this test is rapidly corrected to normal levels. The serum calcium clearance rate varies inversely with age in great measure. For this reason the test is possibly most ideally suited for use in the pediatric age groups, notwithstanding 24 successful trials in 15 adult patients in congestive failure.

ACKNOWLEDGMENT: We wish to thank Osborne A. Brines, M.D., and Anthony Nolke, M.D., for assistance and courtesies extended to us.

REFERENCES

1. **Bronner, F.**, and **Harris, R. S.**: Ann. New York Acad. Sci., **64**, 314, 1956.
2. **Bronner, F., Harris, R. S., Maletskos, C. J.**, and **Benda, C. E.**: J. Clin. Invest., **35**, 78, 1956.
3. **Gubner, R. S.**, and **Kallman, H.**: Am. J. Med. Sci., **234**, 136, 1958.
4. **Hansard, S. L., Comar, C. L.**, and **Davis, G. K.**: Am. J. Physiol., **177**, 383, 1954.
5. **Nalbandian, R. M., Gordon, S., Campbell, R.**, and **Kaufman, J.**: Harper Hosp. Bull., **14**, 328, 1956.
6. Iidem: Am. J. Med. Sci., **233**, 503, 1957.
7. **Nalbandian, R. M., Gordon, S.**, and **Kaufman, J.**: Ibid., **234**, 391, 1957.
8. **Page, E.**, and **Real, J. D.**: Circulation Res., **3**, 501, 1955.
9. **Sapeika, N.**: Arch. Internat. Pharm. Therap., **97**, 373, 1954.
10. **Smith, P. W.**, and **Grinnell, E. H.**: Fed. Proc., **14**, 387, 1955.
11. **Thomas, R. O., Litovitz, T. A., Rubin, M. I.**, and **Geschickter, C. F.**: Am. J. Physiol., **169**, 568, 1952.

SUMMARIO IN INTERLINGUA

Le Test Del Tolerantia Pro Calcium-Digitalis: Un Breve Summario Con Derivation De Formulas De Utilitate Clinic

1. Le litteratura, le principios, e le datos experimental e altere del prime 24 essayos clinic del test de tolerantia a calcium-digitalis es summarisate brevemente, e referentias pertinente es citate.

2. Le *efficace* e *immediate* control del punctos terminal electrocardiographic, signos de intoxication a digitalis provocate per le action de calcium e digitals, per le uso de Na_2EDTA es discutite. Labores experimental de natura confirmatori es citate.

3. Es derivate 3 formulas (Nos. 6, 12, e 19) de utilitate clinic. In conjunction con datos quantitative ab le test del tolerantia a calcium-digitalis, exemplos hypothetic del uso de iste formulas es offerite in le calculation del maximos non-riscose de doses complemental de digitalis.

4. Le test del tolerantia pro calcium-digitalis es destinate al uso in *incommun* problemas clinic de digitalisation. Illo ha essite usate a bon successo pro differentiar, per exemplo, si arrhythmias in casos de disfallimento cardiac es le consequentia de inadequate digitalisation o de intoxication a digitalis. Le test es etiam usabile pro digitalisar un patiente, quando isto es therapeuticamente indicate, usque al nivello del maximo non-riscose, justo infra le nivello del intoxication a digitalis.

5. Le transiente hypercalcemia inducite in le execution del test es rapidemente corrigibile a nivellos normal. Le clearance de calcium seral varia in grande mesura inversemente con le etate del patiente. A causa de iste facto il es possibile que le test es le plus idealmente appropriate al uso in patientes de etates pediatric, in despecto del facto que 24 essayos ha essite effectuate a bon successo in 15 patientes adulte qui se trovava in disfallimento congestive.

SUMMARIO IN INTERLINGUA

(See page 168 for original article)

Atypic Responsas Pressori Al Postura Erecte E A Exercitio In Patientes Con Stenosis Mitral O Aortic

1. Alterationes del pression sanguinee systolic, provocate per un test standard de tolerantia pro exercitio in le forma de ambulation, esseva analysate in subjectos normal e in patientes con varie typos de morbo cardiac. Hypotension in effortio e resalto de restablimento esseva notate frequentemente in patientes con stenosis del valvula aortic o del valvula mitral e a vices in patientes con cargas de volumine intacte.

2. In patientes con regurgitation mitral, hypotension sub effortio esseva minus commun, ben que le resalto de restablimento esseva tanto frequente como in casos de stenosis mitral.

3. Post commissurotomia mitral, le pression systolic medie sub effortio retornava a nivellos normal in patientes in qui le operation habeva effectuate un bon resultato.

4. Alterationes inappropriate del resistentia systemo-vascular in relation al disponibile rendimento cardiac es probabilemente responsabile pro le atypic responsas pressori durante effortio in postura erecte.

ANGIOCARDIOGRAPHY: AN AID FOR THE EARLY DIAGNOSIS OF BRONCHOGENIC CARCINOMA

By Harold A. Lyons, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

AND

Franco Vertova, M.D.
RESIDENT IN RADIOLOGY

(From the Department of Medicine, State University of New York Downstate Medical Center, Brooklyn, New York)

After the courageous pioneer work of Forssman (1929), the injection of opaque contrast media into the venous system for vascular visualization was used mainly for the study of the pulmonary circulation (Lopo de Carvalho, Egas Monis and Almeida Lima[23] and Lopo de Carvalho, Egas Monis and Saldanha[24]). The technique was then improved, but its application was limited to the study of the heart and mediastinum (Castellanos, Periras and Garcia[9] and Steinberg and Robb[49]). Finally, after a lapse of about 10 years, interest in the application of the method to the study of vessels of the lungs was aroused (Neuhof, Sussman and Nabutoff[30] and Soave and Salen[44]). Utilization for the diagnosis of lung tumors was stressed, but again interest was directed to the question of mediastinal involvement and the criteria for operability (De Giuli[13], Fisher[16], Rosenbloom[36], Schissel and Keil[39], Steinberg and Dotter[46], Steinberg and Robb[49], Sussman[50], and Turano[55]).

The use of angiocardiography for the study of pulmonary tumors has been discussed by a number of investigators (Keil, Voelker and Schissel[22], Neuhof, Sussman and Nabutoff[30], Soave and Salen[44], and Steinberg, Dotter and Andrus[48]). Opacification of the vascular pattern in the pulmonary fields provided useful diagnostic and prognostic information. Later, the radiological anatomy of the pulmonary artery and of the major and minor branches was further studied (Papillon, Lournia and Chambelland[31]). Fundamental investigations were done by Mathes, Holman and Reichert[25] and subsequently, by Appleton[3]. The entire pulmonary arterial tree was visualized and the segmental divisions and the smaller branches were identified and characterized so that their involvement by disease could be recognized. Variations from the normal were found in many instances of disease (Steinberg[45]).

In acute pulmonary infections, angiocardiography is mainly of academic interest. Keil and Schissel[22] have noticed an increase in the lung vascularity in unresolved pneumonia. In lung abscess and bronchiectasis, reduced vascularization is present in necrotic areas with a contrasting increase in vascularization in the pneumonic regions. In pulmonary tuberculosis increased vascularization is noted with exudative lesions but a decrease is noted with productive, caseous or cavitary disease (De Coster[12]).

In fibrothorax marked cardiovascular distortion may be shown.

Bullae in emphysema may be delineated more definitely by angiocardiography than by any other radiologic method. When pulmonary hypertension is present, there is a characteristic marked attenuation of the secondary and tertiary branches of the pulmonary arteries with contrasting dilatation of the main branches.

Other changes in the pulmonary vascularization outlined by contrast media are noted in atelectasis. In this condition there is diminished vascularization with crowding together of the lobar and segmental branches. Similar findings have been noted in emphysema ("winter tree pattern"). In malignant pleural mesothelioma one may see deformity of the main pulmonary artery. In pulmonary embolism an abrupt disappearance of the opacification of the involved pulmonary vessel is noted. A bronchopulmonary sequestration may be established when an aberrant vessel is visualized. Displacement of the vessels occurs in pulmonary kyphoscoliosis. In general, a lack of deformity of the arterial structure is noted with metastatic lesions of the lung. This becomes a differential diagnostic sign. Occlusions of pulmonary peripheral branches occur with granulomatous disease such as silicosis, tuberculosis and actinomycosis of the lung. The description of these abnormalities is presented for its bearing on interpretation of findings present with a bronchogenic carcinoma. The findings associated with primary lung cancer are to be described. These angiocardiographic findings are sometimes the first and only diagnostic signs of a primary cancer. They have an almost pathognomonic appearance which, when recognized, may lead to the proper diagnosis. Confirmatory studies, of course, are needed.

Many authors (Abbott, Hopkins and Leigh[1], Benda, Marcha and Hangusae[5], Bompiani[6], De Giuli[13], Rosenbloom[36] Steinberg[45], Steinberg and Dotter[46], Sussman and Grishman[51], and Turano[55]) have already stressed the importance of this diagnostic method for the visualization of mediastinal involvement by a tumor mass or by lymph nodes. Complete or partial obstruction of the subclavian vein may be demonstrated. Compression of the superior vena cava is a frequent finding when it is distorted by a tumor mass or by metastatic lymph nodes. This finding is not pathognomonic of neoplasm, since tuberculosis, actinomycosis, inflammatory lymphadenopathy, lymphoma of the mediastinum and other granulomatous processes may produce the same angiocardiographic finding. Often a compression defect displacement or distortion of the main branches of the pulmonary artery is an associated or a single finding. Invasion of the vena cava, the subclavian artery or of the brachiocephalic branches, or occlusion of the main pulmonary artery proximal to the bifurcation of the right side and within 1.5 cm. from the origin of the left main artery, are definite evidence of mediastinal masses. Invasion of the pericardium indicates an inoperable situation (Amudsen and Sorensen[2], De Clercq *et al.*[11], Slesser, Britt and Freer[41], Soave[42], Soave and Salen[44] and Weiss *et al.*[56]). According to Dotter and Steinberg[14] the absence of these criteria is not an absolutely valid measure of operability. But they maintain that angiocardiography is of value to assess inoperability which cannot be determined by other means.

Angiocardiography helps also in the diagnostic evaluation of other types of mediastinal problems, especially primary abnormalities of the vascular structures. Aneurysm of the great ve-

sels, prominence of the pulmonary artery, anomalous pulmonary venous return, and other conditions, are often misinterpreted by other techniques even after many roentgenographic examinations, and only by their visualization with opaque contrast media is the true nature of the condition established.

This report is written to stress the application of this procedure for the diagnosis of pulmonary carcinoma.

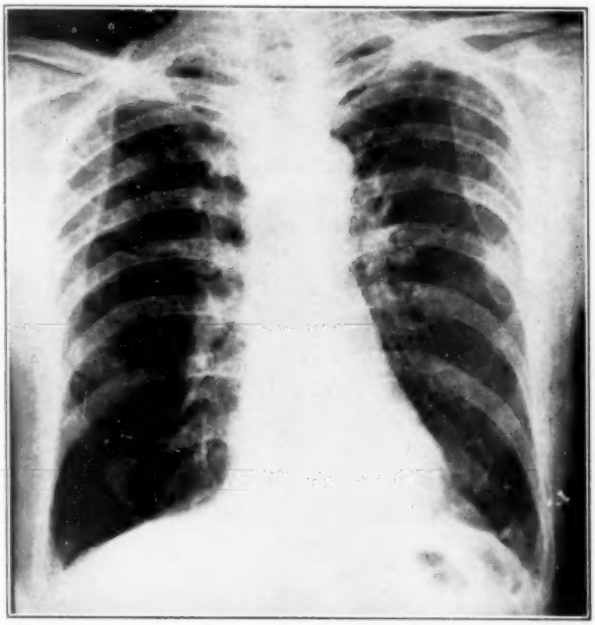


Fig. 1.—The posterior-anterior chest roentgenogram of Case 1. Fibrotic strands can be noted in the left upper lobe, and emphysematous areas at both bases.

The application of angiocardiography for the diagnosis and prognosis of bronchogenic carcinoma has also been found to be most helpful. A large number of advanced cases of carcinoma of the lung have been studied, but these are not the subject of this discussion. The discussion will be concerned with those patients in whom the diagnosis of a bronchogenic carcinoma was first suggested by the angiocardiographic study. Three illustrative cases are presented:

Case Reports. CASE 1. A 75-year-old patient was admitted to the hospital with a history of cough productive of white-greenish sputum for the past 3 years. The cough became worse during the past year. A chest roentgenogram was read as "residual fibrotic strands of infiltration in the apical posterior segment of the left upper lobe" (Fig. 1). The only other findings of importance were three or four Papanicolaou smears read as grade III positive and one as grade IV. Bronchoscopy and angiocardiography were performed the same day. On bronchoscopy, a tiny nodule to the left of the carina was noted, but an attempt at biopsy failed. Angiocardiography showed a complete obstruction of the left upper lobe pulmonary artery. The pulmonary circulation was otherwise normal except for dispersion of vessels at the left lower lobe due to an emphysematous bulla (Fig. 2).

Interpretation. The occlusion of this left upper lobe artery was due to extrinsic pres-

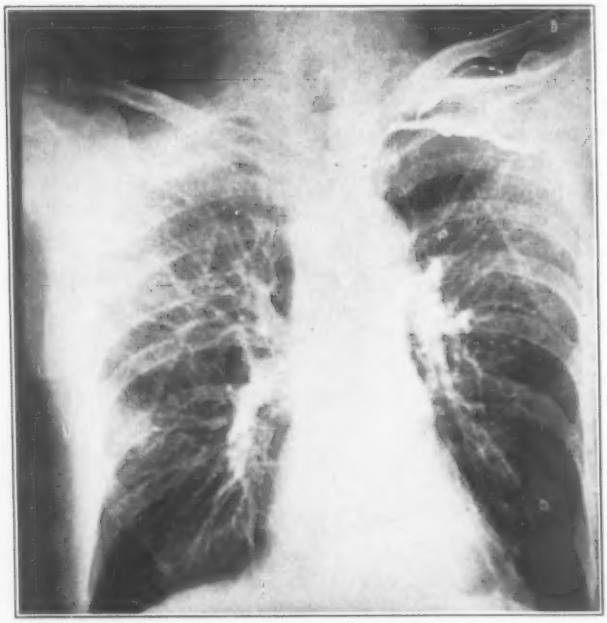


Fig. 2.—The angiocardiographic posterior-anterior film made at 2 seconds. One can note the occlusion and deformity of the left upper lobe pulmonary artery branch.

Fig. 3.—The posterior-anterior angiocardiographic film of Case 2 made at 3 seconds showing the occlusion of the left upper lobe artery and deformity of the area of division with complete absence of opacification of the left upper lobe. These composite findings certainly suggest bronchogenic carcinoma.

sure and this finding, with the report of grade IV cytology, indicated a bronchogenic carcinoma. This interpretation was confirmed later by the clinical course and the necropsy findings of a bronchogenic carcinoma originating in the left upper lobe bronchus.

CASE 2. A 45-year-old man who was a moderate smoker had a chronic cough. One week before admission to the hospital he was treated for pneumonia. A 15-pound weight loss associated with fatigue and exertional dyspnea had progressively appeared over the past year. He was admitted for diagnostic purposes. Multiple sputum examinations and sputum cultures for acid-fast bacteria were negative. The chest roentgenogram was read as showing "foci of infiltration involving the anterior segment of left upper lobe and superior and inferior division lingula. These findings are consistent with pulmonary tuberculosis." The following day a bronchoscopic examination visualized a pale and edematous left upper lobe orifice. The bronchial mucous membrane was pale in all areas seen. Increased secretions were noted on the left side. The bronchial aspirate, on cytologic examination, failed to show malignant cells. Later, an anterior scalene node biopsy was reported as normal. Angiocardiography was then performed. This examination was interpreted as follows: "The left upper lobe pulmonary arterial branches demonstrate poor to absent opacification in the area of infiltration. This is even better demonstrated in the left anterior oblique position than in the posterior-anterior view. Also this artery appears displaced downward and laterally by a mass."

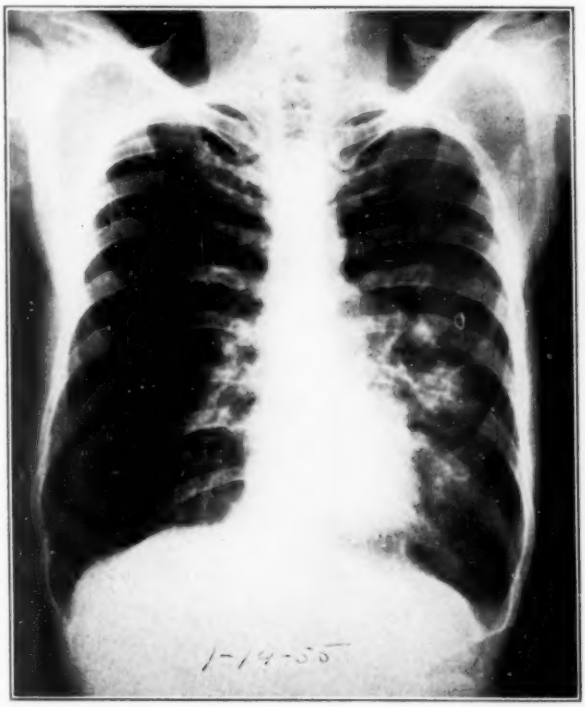


Fig. 4.—The posterior-anterior chest roentgenogram of Case 3 demonstrating infiltrates in the left lower lobe and lingula extending from the hilar regions with some areas of increased radiolucency suggesting honeycombing. Bronchiectasis and pneumonitis were suspected on this study.

Interpretation. The presence of thrombosis of the pulmonary artery branches of the left upper lobe associated with pneumonitis is a frequent finding in pulmonary tuberculosis. The significance of the finding cannot be further elucidated by the angiocardiographic

examination alone, but the questionable mass presents the distinct possibility of a bronchogenic carcinoma (Fig. 3).

The patient transferred to another hospital, and a definite diagnosis, on the basis of the angiocardiographic study, of a left upper lobe bronchogenic carcinoma was made. A left pneumonectomy was done at the other hospital and an adenocarcinoma of the left upper lobe was found.

The sputum studies, including smears, cytologic examination and cultures, were negative. The chest roentgenogram showed honeycombing and highlighting involving both lower lobes (Fig. 4). Bronchiectasis was suspected. A bronchogram was attempted but because of hypersensitivity, it was discontinued. Skin tests with fungal antigens and tuberculin were made. A positive reading was obtained with tuberculin. An angio-

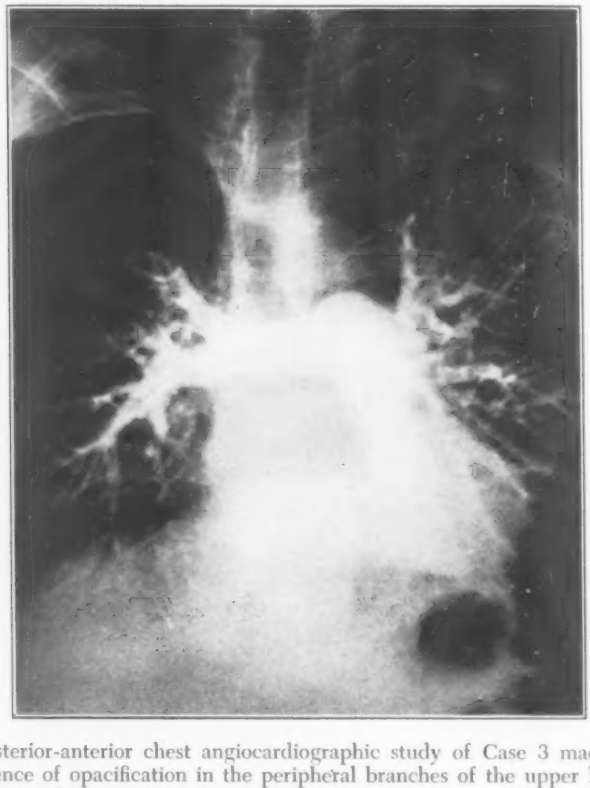


Fig. 5.—The posterior-anterior chest angiocardiographic study of Case 3 made at 3 seconds showing the absence of opacification in the peripheral branches of the upper lobe, the irregularity of the left upper lobe branch and its rather abrupt termination. This is highly suggestive of a neoplastic infiltrative lesion in this area.

CASE 3. A 54-year-old man was admitted because of cough and weight loss. Three years prior to admission, a bowel resection for cancer of the colon had been done at another hospital. Nine months before admission the patient had developed a chronic cough. He was studied at another hospital without a diagnosis being established. Seven months before admission to this hospital the patient experienced frequent hemoptysis.

cardiographic study was made. This procedure gave the following findings: "There appears to be an interruption to the flow of contrast media in the artery to the left upper lobe. This is particularly well seen on the 4-second serial roentgenographic exposure. The right upper lobe appears to have a normal circulation as contrasted with the left upper lobe. The appearance defines an interruption to the flow of contrast media in

the artery of the left upper lobe. The irregularity of the vessel indicates an obstructing invasive process affecting this artery (Fig. 5). Mediastinal vascular structures are not involved by the neoplasm as indicated by abnormalities of the superior vena caval opacification, as seen in earlier films."

The patient progressively deteriorated. A month later, a mass in the rectum was found on examination, and a tissue biopsy showed this to be an adenocarcinoma.

The presence of obstructive emphysema and cardiac decompensation prevented any operation. The patient was readmitted 9 months later and died the next day. Necropsy showed the presence of two carcinomas, a bronchogenic carcinoma and an adenocarcinoma of the rectum.

Discussion. These case reports are illustrative of the value of angiocardiography in demonstrating a pulmonary new growth. Our experience has been so fruitful that this examination has been made a routine procedure for those patients in whom the diagnosis is unresolved, and for whom exploratory thoracotomy is strongly considered.

With the history, physical examination, chest roentgenogram, tomography, bronchoscopy, bronchography, cytologic examinations, the physician can establish the diagnosis of lung cancer in the majority of cases. The question of operability is sometimes a problem. Angiocardiography is an important aid. It not only supplies information of areas of extension and involvement, but also offers a functional preoperative estimate which is helpful to the surgeon.

The procedure is most useful for those patients for whom all the diagnostic methods employed fail to establish a diagnosis. The involvement of the vascular pattern of the lungs by tumor is often an early and constant finding. The vascular irregularity may occur before symptoms are noted. Bronchography, in instances of peripheral lesions, is useless. The incomplete and irregular filling of the peripheral bronchial branches does not allow a final judgment to be made. Opacification of the vascular tree of the lungs can detect smaller areas of involvement. In general, angiocardiographic findings are more definite than either bronchoscopic or bronchographic examinations for the peripherally located lesions. The method confirms the findings of all other examinations (Scarinei and Zucconi[38]). Some authors (Hertrog *et al.*[18], Scarinei and Zucconi[38], and Scozia, Centralla and Lucarelli[40]) state that irregularity and nonfilling of a vessel may result from an abnormality of pulmonary function. They suggest that anoxia in segmental areas of the lung causes occlusion and diminution in the supply of blood. Although this may occur, it will not produce the abrupt occlusions and the vascular irregularities observed with lung cancer.

The vascular arrangement is displaced and compressed by a benign tumor, but practically never occluded, constricted, distorted and invaded as with malignant lesions. The veins are invaded and occluded more rapidly by the process but are also more difficult to visualize by the usual angiocardiographic technique.

In the experience of Papillon and Pinet[32], a distorted stenotic or occluded branch of a pulmonary artery, when clearly identified, is pathognomonic of primary malignancy. A completely normal arterial tree, on the other hand, cannot exclude a malignancy. No patterns distinguish the histologic type of carcinoma. Errors in diagnosis have been reported, one in which a broncholith was the lesion and in another because of a submucosal osteochondroma (Schissel and Keil[39]). Embolization may give the same angiocardiographic appearance but the distortion of the vessel is minor and

the associated clinical findings help to make the exact diagnosis.

In very peripheral lesions, selective angiocardiography may be required for anatomical study of the circulation. The method was first described by Jönsson, Braden and Karnell[20]. Contrast medium is introduced directly into branches of the pulmonary artery. Recent studies (Mattos *et al.*[26] and Rimimi and Duomarco[34]) with this technique, however have indicated that it is not preferable to the usual angiocardiographic technique since it is not physiologic. It is superior nevertheless for anatomic delineation and gives better visualization of minor alterations. That the defects of an arterial branch are due to increase in the peripheral resistance of the vascular segment cannot be excluded by this method. Italian authors (Campitelli[8], Giacobini, Simonette and Tomiselli[17] and Tomiselli[54]) have studied the application of simultaneous angiocardiopneumonstratigraphy with no evident success. Tomography is inferior to angiocardiography for defining the vascular pattern. It cannot demonstrate the small vascular defects which occur with a bronchogenic carcinoma.

Summary. This study shows the value of angiocardiography as an aid in the early diagnosis and prognosis of bronchogenic carcinoma. This diagnostic technique is of particular value for the peripheral lesion, where other findings may be inconclusive. Confirmation of the diagnosis by clinical, laboratory, and tissue studies is not to be neglected. The important fact is that angiocardiography may and can be the first technique to establish an early diagnosis of a bronchogenic carcinoma.

Angiocardiography also supplies additional information for a more complete evaluation of the patient.

REFERENCES

1. **Abbott, O. A., Hopkins, W. A.,** and **Leigh, T. F.**: J. Thoracic Surg., **18**, 869, 1949.
2. **Amudsen, P.,** and **Sorensen, E.**: Acta radiol., **45**, 185, 1956.
3. **Appleton, A. B.**: Lancet, **2**, 592, 1944.
4. **Battessati, M., Soave, F., Tagliaferro, A., Macorini, M., Oliva, L.,** and **Piarra, A.**: Minerva méd., **41**, 633, 1950.
5. **Benda, R., Marcha, M.,** and **Hangusae, J.**: Bull. et mém. Soc. méd. hôp. Paris, **70**, 417, 1954.
6. **Bompiani, C.**: Radiol. med., **37**, 200, 1951.
7. Idem: Ibid., **41**, 1, 1955.
8. **Campitelli, M.**: Arch. radiol., **2**, 389, 1953.
9. **Castellanos, A., Periras, R.,** and **Garcia, A.**: Arch. Soc. Estud Clin. Habana, 1937.
10. **DeBakey, M. D., and Ochsner, A.**: Surgery, **32**, 877, 1952.
11. **De Clercg, F., De Coster, A., Melot, G., Bollaert A., Dumont, A.,** and **Dupres, A.**: Acta chir. belg., **52**, 95, 1953.
12. **De Coster, A.**: Acta cardiol. (Bruxelles), **9**, 424, 1954.
13. **De Giuli, G.**: Nuovi messi di indagine nello studio del mediastino. Semiotica angiocardiografica. Atti XVII Congresso Nas. di Radiologia Medica, 1952.
14. **Dotter, C. T.,** and **Steinberg, I.**: Angiocardiography. New York: Paul B. Hoeber, Inc., 1951.
15. **Dotter, C. T., Steinberg, I.,** and **Holmes, C. W.**: Am. J. Roentgen., **64**, 222, 1950.
16. **Fisher, A. D.**: Dis. Chest, **28**, 651, 1955.
17. **Giacobini, E., Simonette, C.,** and **Tomiselli, M.**: Clinica Nuova, **12**, 22, 1951.
18. **Hertrog, P., Israel, R., Toty, L.,** and **Personne, C.**: J. franc. méd. et chir. thorac., **6**, 450, 1952.
19. **Hoffheins, H. J.**: Thoraxchirurgie, **3**, 132, 1955.
20. **Jönsson, G., Braden, B.,** and **Karnell, J.**: Acta radiol., **32**, 486, 1949.
21. **Keil, P. G.,** and **Schissel, D. J.**: J. Thoracic Surg., **20**, 62, 1950.

22. **Keil, P. G., Voelker, C. A.,** and **Schissel, A. J.:** Am. J. Med. Sci., **219,** 301, 1950.
23. **Lopo de Carvalho, Egas Monis,** and **Almeida Lima:** Presse méd., **40,** 1098, 1932.
24. **Lopo de Carvalho, Egas Monis,** and **Saldanha, A.:** J. Radiol. et electrol., **16,** 469, 1932.
25. **Mathes, M., Holman, E.,** and **Reichert, F. L.:** J. Thoracic Surg., **1,** 339, 1932.
26. **Mattos, A. D., Lisboa, R. M., Rocha M.,** and **Jannurri, A..** Rev. brasil. tuberc., **24,** 831, 1956.
27. **Monod, O.,** and **Katel, E.:** Poumon. (Paris), **6,** 329, 1950.
28. Iidem: Presse méd., **59,** 574, 1951.
29. **Nabutoff, R. A.:** Ann. Surg., **3,** 270, 1951.
30. **Neuhof, H., Sussman, M. L.,** and **Nabutoff, R. A.:** Surgery, **25,** 178, 1949.
31. **Papillon, J., Lournia, J. C.,** and **Chambelland J.:** J. radiol. et electrol., **33,** 213, 1952.
32. **Papillon, J.,** and **Pinet, F.:** Fresse méd., **64,** 1, 1956.
33. **Pons, Eschapasse,** and **Degoy:** J. radio. et electrol., **37,** 556, 1956.
34. **Rimini** and **Duomarco:** Presse méd., **64,** 1582, 1956.
35. **Robb, G. P.,** and **Steinberg, I.:** Am. J. Roentgen., **41,** 1, 1939.
36. **Rosenbloom, S. E.:** Ann. Int. Med., **31,** 470, 1949.
37. **Santy, P., Berard, M., Papillon, J.,** and **Lournia, J. C.:** J. franc. méd. et chir. thorac., **5,** 1, 1951.
38. **Scarinci, C.,** and **Zucconi, C.:** Riforma med., **67,** 349, 1953.
39. **Schissel, D. J.,** and **Keil, P. G.:** Am. J. Roentgenol., **67,** 51, 1952.
40. **Scozia, A., Centralla, G.,** and **Lucarelli, M.:** Arch. tisiol., **2,** 10, 1956.
41. **Slesser, B. V., Britt, R. G.,** and **Freer, J. L.:** Thorax, **9,** 91, 1954.
42. **Soave, F.:** Accademic Medica, **65,** 171, 1950.
43. **Soave, F.,** and **Possenti, B.:** Minerva chir., **11,** 793, 1956.
44. **Soave, F.,** and **Salen, E. F.:** Chirurgia, (Milano), **4,** 209, 1949.
45. **Steinberg, I.:** Am. J. Surg., **89,** 215, 1955.
46. **Steinberg, I.,** and **Dotter, C. T.:** Brit. J. Radiol., **22,** 567, 1949.
47. Iidem: A.M.A. Arch. Surg., **64,** 10, 1952.
48. **Steinberg, I., Dotter, C. T.,** and **Andrus, W. de W.:** Surg., Gynec. & Obst., **90,** 45, 1950.
49. **Steinberg, I.,** and **Robb, G. P.:** Am. Rev. Tuberc., **38,** 557, 1938.
50. **Sussman, M. L.:** Am. J. Roentgenol., **58,** 584, 1947.
51. **Sussman, M. L.,** and **Grishman, A.:** Arch. Int. Med., **2,** 102, 1947.
52. **Taiana, J. A.,** and **Aracaina Zorragim:** Minerva chir., **10,** 61, 1955.
53. **Talbot, T. J.,** and **Silverman, J. J.:** Am. Heart J., **48,** 146, 1954.
54. **Tomiselli, M.:** Progress Med., **9,** 458, 1953.
55. **Turano, L.:** Essai angiocardiographique des alterations vasculaires et circulatoires dans quelques affections mediastinales. Acta VII Con Internat. Radiol., Copenhagen, 1953.
56. **Weiss, A. G., Schmidt, C., Wits, J., Hollender, L.,** and **Koebele, F.:** Presse med., **57,** 1189, 1949.
57. **Weiss A. G.,** and **Wits, J.:** Semaine hôp. Paris, **27,** 3834, 1951.
58. **Weiss, A. G., Wits, J., Hollender, L.,** and **Koebele, F.:** J. radiol. et electrol., **31,** 616, 1950.

SUMMARIO IN INTERLINGUA

Angiocardiographia: Adjuta In Le Precoce Diagnose De Carcinoma Bronchogenic

Le presente studio demonstra le valor de angiocardiographia como adjuta in le precoce diagnose e in le prognose de carcinoma bronchogenic. Le technica diagnostic es de valor special pro le lesion peripheric, ubi altere constatationes es frequentemente inconclusive. Confirmation del diagnose per studios clinic, laboratorial, e histologic non debe esser negligite. Le facto importante es que angiocardiographia es capace a funger como le prime technica que establi un diagnose precoce de carcinoma bronchogenic.

Angiocardiographia provide etiam informationes additional pro un plus complete evalutation del patiente.

RED CELL Na AND K IN CONGESTIVE HEART FAILURE, ESSENTIAL HYPERTENSION AND MYOCARDIAL INFARCTION

By Giuseppe D'Amico, M.D.*
DEPARTMENT OF MEDICINE, UNIVERSITY OF MILANO, ITALY

Several investigators have studied concentration of potassium in red blood cells in relation to that present in cells of other tissues. On the other hand, little is known of erythrocyte sodium and of its relationship to intracellular sodium in general.

The behavior of Na and K in the erythrocytes and plasma of 34 patients with congestive heart failure, 10 patients with myocardial infarction, 5 subjects with essential hypertension and of 25 normal subjects was investigated to find out how much information on electrolyte balance could be obtained by means of these relatively simple techniques.

Methods. Fifteen milliliters of blood were removed from the antecubital vein by means of a heparinized syringe, with a minimum of stasis. A portion of blood was hemolyzed with water while other portions were centrifuged to separate plasma and obtain hematocrit value. Sodium and potassium were determined in laked blood and plasma with a flame photometer Beckman model B. Standard solutions were prepared according to Mosher *et al.*[24]. Concentration of Na and K were calculated using the formula

$$E_e = \frac{E_w - E_p\,(I - V)}{V}$$

where E_e is the concentration of the electrolyte in red cells, expressed in mEq. per L. of cells, E_w is its concentration in whole blood (mEq./L.), E_p is its concentration in plasma (mEq./L.), and V is the hematocrit value (%). The determination of red cell electrolytes by difference between total blood and plasma values avoids the error due to "trapped plasma" except for a small change in the hematocrit reading (about 0.3% of packed cell volume). This error was disregarded. Water content of erythrocytes was determined after drying in oven at 120° C. to constant weight and expressed as % of cell weight.

Results. Values for plasma and red blood cell Na and K content of 25 normal subjects are given in Table 5 and are in good agreement with previous reports[11,13,16,18,29]. Values obtained in 34 cases of congestive failure are given in Tables 1 and 5. The subjects were divided into 3 groups: I) patients with mild failure; II) with failure of medium gravity; III) with severe failure. Because little difference was found between patients with severe dyspnea, but without signs of extracellular fluid retention and those with severe peripheral edema, but without signs of pulmonary congestion or left ventricular failure, no distinction was made between these 2 types in calculating average values in Table 5. In most patients, concentration of Na and K in plasma and of K in red cells was in the normal range. Only in a few patients a slight hyponatremia was noted. On the contrary, the mean concentration of erythrocyte Na was significantly ($P<0.01$) increased in all patients with failure. Except in rare cases this increase was proportional to degree of failure, without distinction between prevalently right or prevalently left failure. Even patients with the least degree of failure had a mean concentration of Na higher than normal subjects ($P<0.05$). The mean

*Present Address: Department of Physiology and Pharmacology, The Chicago Medical School, Chicago 12, Illinois.

concentration of erythrocyte K in patients of groups I and II was in the normal range, while in patients of group III with most severe clinical picture, the erythrocyte K also was significantly increased ($P<0.05$). This rise in Na and K was due most likely to increased amount of electrolytes and not to dehydration of the erythrocyte, since the water content of red cells in 7 patients with congestive failure was not significantly different from normal (Table 2). Concentrations of plasma and erythrocyte Na and K in 10 subjects with myocardial infarction, without failure, were not significantly different from those found in normal subjects (Tables 3 and 5). Only in 2 cases abnormally high values of cellular Na were found: in both cases the determinations were performed 5 days after the coronary occlusion. Tables

TABLE 1.—CONCENTRATION OF SODIUM AND POTASSIUM IN PLASMA AND ERYTHROCYTES OF CARDIAC PATIENTS WITH CONGESTIVE FAILURE

	Case No.	Type*	Plasma (mEq./L. of plasma or cells) Na	Plasma K	Erythrocyte Na	Erythrocyte K
GROUP III†	1	V.D.	133.0	3.1	51.7	99.3
	2	M.S.	142.0	4.0	36.2	106.1
	3	C.P.	135.0	4.2	41.2	97.8
	4	V.D.	144.5	5.4	31.8	102.9
	5	V.D.	144.0	5.0	41.7	95.6
	6	M.S.	147.0	4.3	47.0	101.0
	7	V.D.	143.6	4.3	51.3	94.0
	8	V.D.	143.0	3.7	45.6	82.6
	9	V.D.	141.0	4.5	45.8	93.5
	10	V.D.	131.0	4.4	53.5	97.1
	11	V.D.	141.7	4.0	39.7	92.8
	12	C.P.	145.2	4.5	43.5	101.8
	13	M.S.	150.1	4.3	43.3	103.9
	14	M.S.	148.5	4.3	11.3	106.0
	15	V.D.	149.4	3.9	20.7	104.9
	16	V.D.	139.0	4.9	28.6	97.5
	17	V.D.	136.7	5.1	21.9	107.8
	18	V.D.	140.0	4.5	44.1	102.8
GROUP II‡	19	V.D.	138.8	3.5	39.2	95.9
	20	M.S.	143.5	4.2	25.9	101.0
	21	V.D.	144.5	4.9	35.7	97.4
	22	V.D.	135.0	4.6	25.0	93.4
	23	M.S.	141.5	4.2	30.5	100.2
	24	V.D.	135.0	4.3	42.9	95.0
	25	M.S.	142.6	5.4	26.4	87.7
	26	V.D.	135.0	4.5	35.7	99.3
	27	V.D.	148.3	6.0	21.4	91.4
GROUP I§	28	M.S.	146.9	3.9	24.6	96.7
	29	V.D.	151.0	5.1	26.1	100.6
	30	V.D.	144.5	4.6	24.5	96.1
	31	M.S.	144.5	5.1	31.5	100.0
	32	M.S.	142.6	3.6	13.2	97.1
	33	V.D.	144.0	4.9	16.0	101.4
	34	C.P.	135.6	4.9	43.3	84.7

*V.D. = Valvular Defect; M.S. = Myocardial Sclerosis; C.P. = Cor Pulmonale.
†Marked left or right failure. Marked oliguria.
‡Moderate left or right failure. Moderate oliguria.
§Mild left or right failure. Mild Oliguria.

TABLE 2.—WATER CONTENT OF ERYTHROCYTES IN NORMAL SUBJECTS AND IN PATIENTS WITH CONGESTIVE HEART FAILURE

Normal (% of cell weight)		Congestive Failure (% of cell weight)
74.90		75.25
70.79		72.36
74.42		71.35
73.40		72.10
70.58		72.83
69.26		70.58
		72.40
72.22	Av.	72.41

TABLE 3.—CONCENTRATION OF SODIUM AND POTASSIUM IN PATIENTS WITH MYOCARDIAL INFARCTION

Case No.	Day of test	Plasma (mEq./L. of plasma or cells) Na	Plasma K	Erythrocyte Na	Erythrocyte K
1	1	150.2	4.3	23.2	94.0
2	1	141.5	4.7	12.7	89.4
3	1	152.0	3.6	15.6	99.2
4	1	139.5	3.6	9.3	115.1
5	5	141.0	4.1	38.3	91.8
6	5	138.0	4.2	44.5	91.2
7	8	142.6	3.9	22.3	102.4
8	15	147.0	4.9	19.0	89.6
9	60	140.4	4.2	20.5	93.4
10	60	147.5	4.6	24.6	78.2

4 and 5 show the values of plasma and erythrocyte Na and K in 5 subjects with essential hypertension without clinical or laboratory signs of renal or cardiac disease. The concentration of red cell Na was found significantly higher than normal ($P<0.01$), while the potassium was normal.

TABLE 4.—CONCENTRATION OF SODIUM AND POTASSIUM IN PATIENTS WITH ESSENTIAL HYPERTENSION WITHOUT RENAL INSUFFICIENCY

Case No.	Plasma (mEq./L. of plasma or cells)		Erythrocyte (mEq./L. of plasma or cells)	
	Na	K	Na	K
1	144.0	3.9	37.5	95.1
2	140.0	4.5	38.3	91.4
3	145.0	4.0	15.0	94.3
4	142.1	4.3	33.5	92.0
5	146.0	4.9	22.2	99.5

TABLE 5.—AVERAGE CONCENTRATION OF SODIUM AND POTASSIUM IN PLASMA AND IN ERYTHROCYTES OF NORMAL SUBJECTS AND OF PATIENTS WITH HEART DISEASE OR ESSENTIAL HYPERTENSION

Type	No. of patients	Plasma (mEq./L. of plasma or cells ± S.D.)		Erythrocyte (mEq./L. of plasma or cells ± S.D.)	
		Na	K	Na	K
Normal	25	145.13 ± 4.06	4.29 ± 0.39	18.37 ± 6.49	95.96 ± 3.99
Congestive failure					
Group I	7			25.60 ± 9.23	96.65 ± 5.25
Group II	9			31.41 ± 6.89	95.70 ± 4.12
Group III	18			38.83 ± 11.7	99.30 ± 6.22
All groups	34	142.00 ± 5.14	4.47 ± 0.60	34.47 ± 11.2	97.80 ± 5.80
Myocardial infarction	10	143.97 ± 4.58	4.21 ± 0.42	23.00 ± 10.9	94.43 ± 9.68
Essential hypertension	5	143.4 ± 2.14	4.32 ± 0.37	29.3 ± 9.17	94.54 ± 2.87

Discussion. CONGESTIVE HEART FAILURE. The values for plasma Na and K are in agreement with those found by other investigators: in spite of the marked sodium retention, the expanded extracellular compartment is either isotonic or, in some cases of severe chronic failure, hypotonic. In contrast with these small changes in plasma electrolytes, there was a significant rise in red cell Na. This poses 2 questions: 1) Is this rise quantitatively related to degree of myocardial failure and of renal retention of Na? 2) Are the changes in red cell electrolytes a reflection of similar changes in the whole intracellular compartment? The values reported in Tables 1 and 5 suggest that, with a few exceptions, a relationship exists between increase in cellular Na and degree of cardiocirculatory insufficiency and in particular between cellular Na and daily urinary output, without regard to development of edema. Of course this correlation is not absolute and, although in the few cases in which water content of red cells was determined, this was not found significantly different from normal, the possibility exists that dehydration of the cell possibly due to therapy (diuretics, digitalis) or other factors may contribute to the apparent increase of erythrocyte Na. The available data do not indicate whether in congestive failure red blood cells retain sodium because they behave as an enlarged but otherwise normal reservoir of the electrolyte or because membrane permeability is altered as a result of the abnormal hormonal situation. In general, any movement of Na across the membrane of muscle

cells is accompanied by movement of K in the opposite direction. This was not true in most severe cases of failure studied in whom the increase of erythrocyte Na was accompanied by an increase of erythrocyte K and the cells became hypertonic in relation to plasma. A similar hypertonicity of muscle cells in congestive heart failure has been reported by other investigators (Elkinton and Squires[7] and Iseri *et al.*[12]) and attributed to metabolic changes due to cellular hypoxia. Although our finding of increased erythrocyte Na in such different diseases as Laennec's cirrhosis, nephrosis and Cushing's syndrome (unpublished), suggests that metabolic alteration responsible for these changes may not be specific, a common denominator such as primary or secondary hyperaldosteronism may exist. Existence of hyperaldosteronism in congestive failure has been suggested by several investigators (Davis *et al.*[5] and Luetscher and Johnson[21]) and Kessler *et al.*[15], reported an increase of erythrocyte Na 30 minutes after intravenous administration of hydrocortisone. The increase of erythrocyte K found in most severe cases of failure, is harder to explain, as it is contrary to results reported by other investigators (Clarke and Mosher[2], Mokotoff, Ross and Leiter[22], Moore *et al.*[23] and Squires, Crosley and Elkinton[28]) who found a decrease of intracellular K of muscle in congestive failure. Although Streeten and Solomon[29] found that administration of ACTH or cortisone increases erythrocyte K concentration in man, while causing a decrease of total intracellular K, unpublished observations in subjects with marked changes of K balance and very low potassemia of various origins suggest that concentration of K in red cells does not necessarily reflect the true state of total body K. This impression is confirmed also by observations of Davidsen and Jensen[4] and of Schwartz and Relman[27], whereas other investigators (Eliel, Pearson and Rawson[6], Hutt[11], Keitel[14] and Lans, Stein and Meyer[18]) reported changes in erythrocyte K in patients with various types of electrolyte imbalance.

MYOCARDIAL INFARCTION. Some investigators (Agnoletto[1] and Tartara and Casirola[30]) reported a rise of plasma K in cases of recent infarct. No changes in the concentration of this electrolyte were found in plasma of our patients, and a rise of erythrocyte K was demonstrated only in one case. The fact that an increase in erythrocyte Na was found 5 days after onset of myocardial infarction could be coincidental, although it should be pointed out that this is a critical time in the course of the disease when danger of acute failure is greatest. Low erythrocyte K concentration (78.2 mEq./L.) found in one patient 2 months after onset of coronary occlusion should be mentioned. In this case the determination was performed because the patient developed signs of digitalis intolerance.

ESSENTIAL HYPERTENSION. A relationship between Na balance and essential or experimental hypertension has long been suspected (Dahl[3], Fregly, Yates and Landis[8], Holley, Elliott and Holland[10], Kylin and Elmquist[17], Lenel, Katz and Rodbard[20], Perera and Blood[25], and Sapirstein, Brandt and Drury[26]). Laramore and Grollman[19] found increased intracellular Na and decreased intracellular K in brain, heart, muscle and skin of rats with renal hypertension; Tobian *et al.*[31,32] reported increased concentration of Na and water in renal arterial wall and in psoas muscle of humans with essential hypertension and obtained a rise of arterial wall sodium in rats made hypertensive with DOCA. Genest *et al.*[9] reported increased

urinary excretion of aldosterone in some subjects with essential hypertension. Although it is difficult to demonstrate a correlation between these data and the demonstrated increase of red cell sodium in essential hypertension, it is suggested that a mild hyperaldosteronism may exist in essential hypertension and be responsible for the observed changes. These observations may be significant because the red cells, contrary to muscle cells and arterial wall, are free of collagen, establishing the fact that sodium increase is intracellular as well as extracellular.

Summary. 1) Plasma and erythrocyte sodium and potassium were determined in 25 normal subjects, 34 patients with congestive heart failure, 10 with myocardial infarction and 5 with essential hypertension. 2) Heart failure appears to be accompanied by a rise in erythrocyte Na, which is proportional to degree of failure and of sodium retention. This rise is not due to dehydration of cells. A rise of erythrocyte K was also observed in most severe cases. 3) No significant electrolytic changes were noted in patients with myocardial infarction. 4) In 3 of 5 cases of essential hypertension the concentration of erythrocyte Na was increased. 5) In spite of the frequent failure to find a correlation between red cell potassium and potassium deficit, these and other unpublished observations suggest that red cell sodium in some way, may reflect changes in sodium balance.

REFERENCES

1. **Agnoletto, A.:** Progresso Med., **9**, 248, 1953.
2. **Clarke, N. E., and Mosher, R. E.:** Circulation, **5**, 907, 1952.
3. **Dahl, L. E.:** Proc. Soc. Exper. Biol. & Med., **94**, 23, 1957.
4. **Davidsen, H. G., and Jensen, K. K.:** Ibid., **74**, 477, 1950.
5. **Davis, J. O., Pechet, M. M., Ball, W. C., Jr., and Goodkind, M. J.:** J. Clin. Invest., **36**, 689, 1957.
6. **Eliel, L. P., Pearson, O. H., and Rawson, R. W.:** New England J. Med., **243**, 471, 1950.
7. **Elkinton, J. R., and Squires, R. D.:** Circulation, **4**, 679, 1951.
8. **Fregly, M. J., Yates, F. E., and Landis, E. M.:** Proc. Soc. Exper. Biol. & Med., **90**, 695, 1955.
9. **Genest, J., Lemieux, G., Davignon, A., Koiw, E., Nowaczynski, W., and Steyermark, P.:** Science, **123**, 503, 1956.
10. **Holley, H. L., Elliott, H. L., Jr., and Holland, C. M., Jr.:** Proc. Soc. Exper. Biol. & Med., **77**, 561, 1951.
11. **Hutt, M. P.:** Am. J. Med. Sci., **223**, 176, 1952.
12. **Iseri, L. T., McCaughey, R. S., Alexander, L., Boyle, A. J., and Meyers, G. B.:** Ibid., **224**, 135, 1952.
13. **Keitel, H. G., Berman, H., and Mac Lachlan, E.:** Blood, **10**, 370, 1955.
14. **Keitel, H. G.:** J. Lab. & Clin. Med., **49**, 267, 1957.
15. **Kessler, E., Nelson, S. S., Elder, N. R., Rosano, C. L., and Nelson, W. P.:** J. Appl. Physiol., **10**, 93, 1957.
16. **Knowles, H. C., Alverson, G., and Rubenstein, E.:** J. Lab. & Clin. Med., **45**, 463, 1955.
17. **Kylin, E., and Elmquist, H.:** Acta med. Scandinav., **88**, 507, 1936.
18. **Lans, H. S., Stein, I. F., Jr., and Meyer, K. A.:** Am. J. Med. Sci., **223**, 65, 1952.
19. **Laramore, D. C., and Grollman, A.:** Am. J. Physiol., **161**, 278, 1950.
20. **Lenel, R., Katz, L. N., and Rodbard, S.:** Ibid., **152**, 557, 1948.
21. **Luetscher, J. A., Jr., and Johnson, B. B.:** J. Clin. Invest., **23**, 1441, 1954.
22. **Mokotoff, R., Ross, G., and Leiter, L.:** Ibid., **41**, 291, 1952.
23. **Moore, F. D., McMurrey, J. D., Parker, H. V., and Magnus, I. C.:** Metabolism, **5**, 447, 1956.
24. **Mosher, R. E., Boyle, A. J., Bird, E. J., Jacobson, S. D., Batchelor, T. M., Iseri, L. T., and Myers, G. B.:** Am. J. Clin. Path., **19**, 461, 1949.

25. **Perera, G. A.**, and **Blood, D. W.**: Am. J. Med., **1**, 602, 1946.
26. **Sapirstein, L. A., Brandt, W. L.**, and **Drury, D. R.**: Proc. Soc. Exper. Biol. & Med., **73**, 82, 1950.
27. **Schwartz, W. B.**, and **Relman, A. S.**: J. Clin. Invest., **32**, 258, 1953.
28. **Squires, R. D., Crosley, A. P., Jr.**, and **Elkinton, J. R.**: Circulation, **4**, 868, 1951.
29. **Streeten, D. H. P.**, and **Solomon, A. K.**: J. Gen. Physiol., **37**, 643, 1954.
30. **Tartara, A.**, and **Casirola, G.**: Progresso Med., **10**, 102, 1954.
31. **Tobian, L.**, and **Binion, J. T.**: Circulation, **5**, 754, 1952.
32. **Tobian, L.**, and **Redleaf, P. D.**: Am. J. Physiol., **189**, 451, 1957.

SUMMARIO IN INTERLINGUA

Natrium E Kalium Del Erythrocytos In Congestive Disfallimento Cardiac, In Hypertension Essential, E In Infarcimento Myocardial

1. Le natrium e le kalium del plasma e del erythrocytos esseva determinate in 25 subjectos normal, 34 patientes con congestive disfallimento cardiac, 10 con infarcimento myocardial, e 5 con hypertension essential.

2. Disfallimento cardiac es apparentemente accompaniate de un augmento del natrium erythrocytic, proportional al grado del disfallimento e al grado del retention de natrium. Iste augmento non resulta de dishydratation del cellulas. Augmentos del kalium erythrocytic esseva etiam observate in le majoritate del casos grave.

3. Nulle significative alterationes electrolytic esseva notate in patientes con infarcimento myocardial.

4. In 3 del 5 casos de hypertension essential, le concentration de natrium in le erythrocytos esseva augmentate.

5. Ben que in multe casos il non esseva possibile demonstrar un correlation inter le kalium del erythrocytes e le deficit de kalium, le presente observationes, insimul con alteres non publicate, suggere que le natrium erythrocytic reflecte, sin que on sape como, alterationes del balancia de natrium.

CENTRAL NERVOUS SYSTEM STIMULATION AND SEDATION WITH DIMETHAZAN

By Robert C. Batterman, M.D.
ASSOCIATE PROFESSOR OF MEDICINE

Arthur J. Grossman, M.D.
ASSISTANT CLINICAL INSTRUCTOR IN MEDICINE

Paul Leifer, M.D.
FELLOW IN MEDICINE

AND

George J. Mouratoff, M.D.
FELLOW, DEPARTMENT OF HOSPITALS

(From the Department of Medicine, New York Medical College-Metropolitan Medical Center, New York, New York)

The value of caffeine and its salts for diverse therapeutic indications has been universally accepted (Goodman and Gilman[4]). Although utilization of these compounds, alone or in combination with other medications is well known, certain shortcomings limit their usefulness and reflect the need for more effective derivatives. The caffeine derivatives available at present are gastric irritants and this intolerance prevents the attainment of optimum dosage for satisfactory therapeutic effectiveness. Even with optimum dosage, their potency leaves much to be desired. It is the purpose of this report to present our experiences with a new caffeine derivative which not only overcomes the above disadvantages but also possesses unusual therapeutic properties.

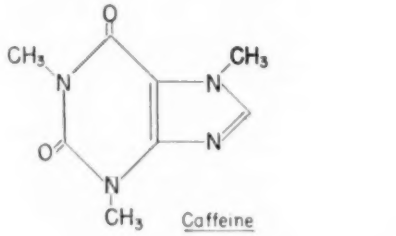
Dimethazan* is 1,3-dimethyl-7-(2′-dimethylaminoethyl) xanthine and differs from caffeine (1,3,7-trimethyl xanthine) by the replacement of the third methyl group (see Fig. 1). Pharmacologic investigation by Blumberg *et al.*[2] details the following: 1) Dimethazan is more than twice as active as caffeine in counteracting pentobarbital hypnosis in mice and rats, 2) the respiratory stimulatory effects are more than twice that of caffeine without the occurrence of locomotor stimulation, or cardiac irregularities, 3) toxicity studies by parenteral route favor Dimethazan.

Our studies in man were done under the following plans: I) Determination of effects following a single intravenous injection. II) Evaluation of central nervous system effects and tolerance when administered orally for the treatment of mental and physical depression.

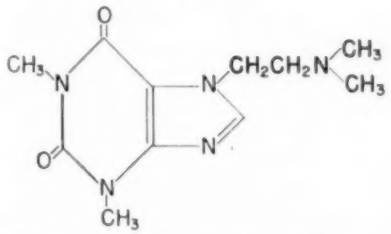
Methods and Results. I. INTRAVENOUS INJECTION. The effects of a single intravenous dose were studied in 66 subjects. All were inmates of a chronic disease hospital and were patients requiring hospitalization because of generalized arteriosclerosis, hemiplegia and various neurologic disorders. The majority were apathetic and lethargic.

*The medication and other aid for this investigation were supplied by Endo Laboratories Inc., Richmond Hill, New York.

They were usually lying in bed without manifesting any interest to their environment, other patients or hospital personnel. One patient, detailed later, was markedly depressed as the result of chronic chlorpromazine therapy. After a control period of observation wherein the blood pressure, pulse rate, respiratory rate, mental status, pupillary size and status of mucous membranes were noted, the subject received 50 to 600 mg. of Dimethazan intravenously. The injection was given over a 2- to 4-minute period and the above observations were repeated at 5-minute intervals until any observable effects had subsided.



Caffeine



7-(2-dimethylaminoethyl) theophylline

Fig. 1.—Chemical structure of Dimethazan.

The effects upon the respiratory rate were transitory in all subjects so affected. However, the effect was consistent in the majority of patients. Fifty-one of the 66 subjects (77%) had an increase in respiratory rate. An associated increase in depth of respiration was also noted in several subjects but was not significant except in a few instances. This, however, was as expected since with only one exception the subjects were free of respiratory depression during the control period and responsiveness of analeptics in such cases is limited.

Case Report. A.W., a 76-year-old man was bed-ridden because of cerebral and generalized arteriosclerosis, right hemiplegia and bilateral amputations. Because of delusions and auditory hallucinations, he received 4 doses of 100 mg. chlorpromazine orally. Within 24 hours he became apathetic, lethargic and nonresponsive to stimuli. The blood pressure was 106/76, respirations 16/min., and the pulse rate 84. Dimethazan, in a single dose of 300 mg. was given intravenously over a 3-minute period. Within 2 minutes the respiration increased in depth and the rate increased to 24 per min. The mental status improved within 5 minutes, reached its peak in 15 minutes and lasted over 4 hours. During this time patient was alert, coherent and responded normally to all stimuli. Blood pressure and pulse rate remained unchanged.

Cerebral stimulation manifested by improvement in mental status, alertness, and restlessness was also transi-

tory. Regardless of dosage, the over-all effect was noted in 56% of the subjects.

With doses above 300 mg. the stimulatory effects in 8 instances appeared to be greater than a therapeutic effect and therefore the occurrence of marked restlessness or an agitated state was classified as an untoward reaction. Whether patients with previous drug depression will manifest the same dose response effects cannot be answered at present. However, experience with the analeptics suggest that patients with sedative or drug depression could tolerate much higher doses of an analeptic without occurrence of signs and symptoms of cerebral stimulation which in a "normal" subject would be classified as toxicity.

No effect was noted upon blood pressure, pulse rate, pupillary size or mucous membrane of the mouth.

II. CENTRAL NERVOUS SYSTEM EFFECTS: ORAL ADMINISTRATION. Since our prime concern was the evaluation of Dimethazan as a stimulant, mental as well as physical, ambulatory patients were chosen at first entirely upon the basis of existence of chronic fatigue, lack of energy, "no pep," tiredness, lethargy, sluggishness, listlessness and apathy. It soon became apparent that in many of these patients it was impossible to separate the problems of anxiety state which ordinarily would be treated with sedatives or tranquilizers. When it was noted that Dimethazan in these patients also evoked a sedative effect, the choice of subjects was expanded to include such patients who might be benefited by sedatives even though "mental and physical stimulation" were not required.

The medication was administered as 100 to 400 mg., 3 to 4 times daily. The duration of therapy, with one exception, varied from 1 to 15 weeks of continuous drug administration. The majority of the trials were for 3 weeks or longer and 13 trials were from 8 to 15 weeks. The one exception stopped the medication after 2 days because of "giddiness" but subsequently took the medication for 3 weeks without the occurrence of any untoward reaction.

Eighty-seven patients for a total of 99 trials received the medication orally. The results according to dosage, stimulatory or sedative effects are summarized in Table 1. Trials with the 200 mg. dosage comprise the bulk of the investigation. Higher dosages were studied primarily for toxicity purposes. Regardless of dosage, a satisfactory stimulatory effect was noted in 57 of the 84 trials (68%) studied for this purpose. Although a higher incidence of effectiveness was noted for the 100 mg. dosage, the number of subjects in this group does not allow statistical comparison. Satisfactory stimulation meant that the patients indicated without qualification that they had one or more of the following: "more pep," "were not tired," "had increased energy," "could do more," and were "more alert." Any lesser effect, where on the basis of subjective analysis there might have been a question, was considered to be unsatisfactory. In each of the satisfactory cases, there was no doubt for both the patient and investigator that good stimulation had occurred. This stimulation occurred in the absence of nervousness, irritability, jitteriness or insomnia. Even though the medication was taken before retiring as was advised in the majority of patients, there was not one instance of sleep disturbance. On the contrary, many of the patients noted that their previous insomnia had subsided and that they were now sleeping better or normally.

Forty-seven trials were observed for possible sedative effects of Dimethazan according to the methods (Batterman *et al.*[1]) described previously. Thirty-

two subjects or 68% had satisfactory daytime sedation with control of the anxiety state or a hypnotic effect, or both, which alleviated various degrees and types of insomnia.

The occurrence of untoward reactions was noted in 5 of the 99 trials for an incidence of 5%. Gastrointestinal complaints were noted in 4 trials but in each instance they were of no significance. An occurrence of "giddiness" with one trial was doubtful since a subsequent trial with the same dosage was free of reactions. Complete blood counts and urine examinations performed on a random basis revealed no alteration.

TABLE 1—STIMULATORY AND SEDATIVE EFFECTS OF DIMETHAZAN

Dose mg.	*No. of Trials*	*No. of Trials*	*Stimulation Satisfactory No.*	*%*	*None*	*No. of Trials*	*Sedation Satisfactory No.*	*%*	*None*
100	15	15	13	86.6	2	4	3	75	1
200	80	67	43	64.2	24	40	26	65	14
300	2	1	1			2	2		
400	2	1			1	1	1		
	99	84	57	67.9	27	47	32	68.1	15

The effectiveness and tolerance of Dimethazan with administration orally in hospitalized patients were studied in 46 subjects. These were inmates of a chronic disease hospital and presented the usual picture of senile dementia with mental depression, confusion, apathy, listlessness or restlessness. The basic diagnosis in all but a few instances was generalized arteriosclerosis with varying degrees of cerebral involvement. Hypertension, multiple sclerosis, parkinsonism and rheumatoid arthritis accounted for the few exceptions. The majority of the patients were over 80 years of age. The initial dose was either 100 or 200 mg. given 4 times daily. Nine subjects began therapy with the 100 mg. dose but in 5 this was increased to 200 mg. dose. This was primarily for purposes of toxicity studies and not because the lower dosage was ineffective. The duration of therapy approximated 3 months or longer in 33 subjects.

The patients included in this study usually vegetate in chronic disease institutions and it is difficult to determine whether sedatives or stimulants are required. It was, therefore, of interest to note that 31 of the 46 patients (67%) regardless of dosage had a satisfactory clinical response. This was manifested by increased alertness, quietness, improvement in personality, greater cooperativeness, less mental depression and easier nursing care. A satisfactory response was noted only after several days. In some patients, 2 or 3 weeks of continuous therapy was necessary before an effect became apparent.

The medication was completely free of any untoward reactions. Complete blood counts, urine examinations and other clinical chemical determinations revealed no abnormality secondary to the medication.

Discussion. It has been recently noted by a special report[3] of the Council on Drugs of the American Medical Association that considerable confusion exists as to the classification of psychotherapeutic drugs. Four major

classifications are given and include I) Antihistamines, II) Central Nervous System depressants, III) Central Nervous System stimulants, and IV) Miscellaneous agents. It was pointed out that "'peace of mind' can also be created in depressed individuals by judicious use of substances that are pharmacological stimulants." Although in our experience this has been noted in an occasional patient with the commonly employed stimulants such as amphetamine or methylphenidate (Ritalin) hydrochloride, the likelihood of attaining an assured sedative or tranquilizer effect with a stimulant is an unusual clinical occurrence. It was, therefore, an unexpected finding to note that Dimethazan, which possesses unquestionable stimulatory effects, might also act as a tranquilizing medication. The impression was gained that when depression was the major factor in the patients' disability then the stimulatory effect was more apparent. On the other hand when excitability, nervousness, jitteriness and other problems related to the anxiety state were to the front then the tranquilizing action was evident. This duo effect resembles a homeostatic or normalizing mechanism which heretofore has been obtained only with combinations of sedatives and stimulants. The advantage of a single medication which possesses both effects is obvious. The sedative action of Dimethazan might explain the absence of central nervous stimulation with nighttime dosage. On the other hand the stimulatory effects offset any excessive daytime sedation such as drowsiness.

Unlike caffeine or other xanthine compounds, this preparation is well tolerated. Gastrointestinal symptoms in spite of chronic administration were of no consequence. Several patients, both ambulatory and hospitalized, had an underlying gastrointestinal condition such as peptic ulcer or hiatus hernia and in no case was there any indication of activation or gastrointestinal intolerance.

The effects of Dimethazan as a respiratory stimulant warrant further clinical evaluation. It is well recognized that individuals without respiratory depression are not ideal subjects for determination of respiratory stimulation. Pharmacologic evaluation of the effects following an intravenous dose of Dimethazan, however, indicated that such a stimulatory effect although transitory, was possible in the majority of subjects. The utilization of this effect for the emergency treatment of a patient with respiratory and cerebral depression secondary to chlorpromazine administration confirmed the clinical possibilities of this preparation. The stimulatory effects upon the respiratory center and cerebral function without alteration of blood pressure and pulse rate, particularly as noted in geriatric patients, suggest that Dimethazan would have considerable value for the purposes of central nervous stimulation.

Conclusions. 1) Dimethazan, a new caffeine derivative, 1,3-dimethyl-7-(2'-dimethylaminoethyl) xanthine, when administered intravenously to 66 geriatric patients results in transitory respiratory and cerebral stimulation in the majority of subjects.

2) The clinical utilization of the respiratory stimulatory effect was confirmed in a patient markedly depressed with chlorpromazine therapy.

3) The oral administration of Dimethazan to 87 ambulatory and 46 hospitalized patients for treatment of mental and physical depression indicated a duo effect of central nervous system stimulation and sedation. This unusual combination of effect with a single chemical preparation offers a unique control of patients with mild

symptoms of depression or anxiety state.

4) Dimethazan is a safe and well tolerated medication with none of the shortcomings of heretofore available caffeine preparations.

REFERENCES

1. (a) **Batterman, R. C., Leifer, P.,** and **Grossman, A. J.:** Am. Pract. & Digest Treat., **7,** 1795, 1956.
(b) **Batterman, R. C., Grossman, A. J., Leifer, P.,** and **Mouratoff, G. J.:** Clinical re-evaluation of Daytime Sedatives. Submitted for publication.
2. **Blumberg, H., Carson, S., Dayton, H. B., Stein, E.,** and **Gordon, S. M.:** Fed. Proc., **17,** 350, 1958.
3. Council on Drugs, American Medical Association, Report of: J. Am. Med. Assn., **166,** 1040, 1958.
4. **Goodman, L. S.,** and **Gilman, A.:** The Pharmacological Basis of Therapeutics, 2nd ed. New York: The Macmillan Co., 1955.

SUMMARIO IN INTERLINGUA

Stimulation Del Systema Nervose Central E Effecto Sedatori Con Dimethazano

1. Dimethazano, 1,3-dimethyl-7-(2′-dimethylaminoethyl)-xanthina, es un nove derivato de caffeina, le qual, quando administrate per via intravenose a 66 patientes geriatric, resultava in un transitori stimulation respiratori e cerebral in le majoritate del casos.

2. Le utilisation clinic del effecto stimulatori super le respiration esseva confirmate in un patiente marcatemente deprimite in consequentia de therapia a chlorpromazina.

3. Le administration oral de Dimethazano a 87 patientes ambulatori e a 46 patientes hospitalisate como tractamento de depression mental e physic revelava un duple effecto de stimulation del systema nervose central e de sedation. Iste combination inusual de effectos in un sol preparato chimic permitte un control quasi ideal in patientes con leve symptomas de depression o de statos de anxietate.

4. Dimethazano es salve e ben tolerate e possede nulle del disavantages del preparatos de caffeina usque nunc disponibile.

ATYPICAL PRESSOR RESPONSES TO UPRIGHT POSTURE AND EXERCISE IN PATIENTS WITH MITRAL OR AORTIC STENOSIS*

By Gordon A. Logan, M.D.
CLINICAL ASSOCIATE, DEPARTMENT OF MEDICINE, UNIVERSITY OF WASHINGTON

AND

Robert A. Bruce, M.D.
ASSOCIATE PROFESSOR OF MEDICINE, UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
SEATTLE, WASHINGTON

Previous studies have revealed unusual pressor responses in some patients with mitral stenosis who have had standard tests of exercise tolerance performed in this laboratory[3]. Similar findings have also occurred in patients with other cardiac lesions, particularly aortic stenosis, but the incidence has not been well defined. It is the purpose of this report to describe these atypical pressor responses to exercise in the upright posture, and to indicate the relative frequency of their occurrence.

Data on blood pressure were obtained from 16 normal adult subjects and 168 patients with various types of cardiovascular disease. These included 45 patients with mitral stenosis who had been subjected to commissurotomy, and who had had exercise tests both before and after operation. Data from these tests were available for study. The last preoperative and best postoperative tests were selected for comparative analysis, since they reflected the maximal degree of improvement from preoperative medical therapy, and the optimal benefit obtained from surgery. Twenty-nine of these patients with mitral stenosis improved following operation, as determined by clinical criteria, and were classified in a "good result" group; the remaining 16 were unchanged, or worse, and were classified in a "poor result" group.

Methods. The standard test of exercise tolerance employed in these studies required the patient to walk on a motor-driven treadmill at 1.7 miles per hour on a 10% grade. He was expected to continue this exertion to the limits of his tolerance, but not for more than 10 minutes. This exertion increased oxygen consumption three to four times above the resting level. Exercise was routinely preceded by a 4-minute rest period during which the patient sat quietly. This was followed by one minute of standing. Observations were continued after exercise for a 5-minute recovery period. Blood pressure was determined every minute during sitting, standing, walking and sitting again by means of a conventional sphygmomanometer. Exercise tolerance was expressed in terms of a physical fitness index (PFI), which was derived from measurements of endurance, average "respiratory efficiency" during exercise, and cumulative heart rate for the first 3 minutes of recovery (Bruce[1]).

"Exertional hypotension" was defined as a failure to increase systolic pressure by more than 10% of the value observed during the fourth minute of rest.† "Recovery rebound" was defined as an increase of more than 15 mm. Hg for the sum of systolic pressures for the first 2 minutes of recovery above the similar sum of systolic pressures observed during the last 2 minutes of walking.‡

*This study was supported, in part, by Grant-in-Aid H 908 C5 from the National Health Institute, United States Public Health Service.

†This value was exceeded by all but one normal subject.

‡The sum of 2 minutes was used, since the rise in pressure occurred during either the first or second minute of recovery. This value was the maximal rebound observed in one normal subject. Rebound in all other normal subjects, save one, was a negative value.

Results. 1. PRESSOR RESPONSES TO STANDING AND WALKING IN NORMAL SUBJECTS. Average values and standard deviations for both systolic and diastolic pressures observed in normal subjects are shown in Fig. 1 from the fourth minute of sitting at rest, through one minute of standing, 10 minutes of walking, and 5 minutes of sitting during recovery. The systolic pressure increased slightly on standing, and gradually rose during the first 4 minutes of walking. Thereafter it remained fairly constant on a plateau about 20 mm. Hg higher than that observed during rest. After exercise, the systolic pressure gradually diminished. There was no significant change in diastolic pressure with either standing or walking at the rate of energy expenditure required for this work load.

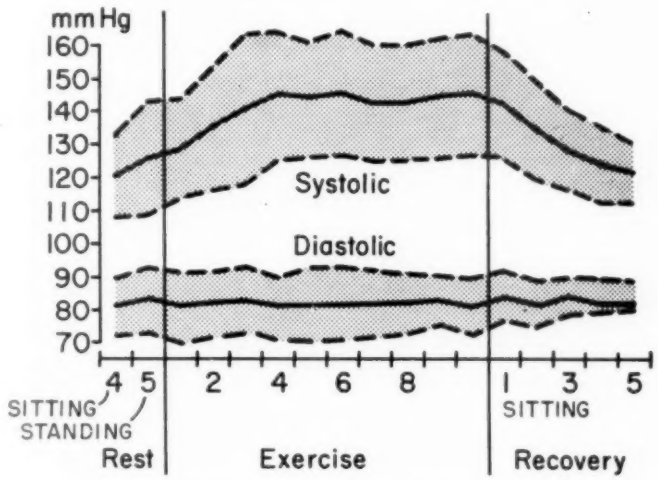


Fig. 1.—Changes in systolic and diastolic pressures in response to standing and walking in 16 normal subjects (Mean ± one Standard Deviation).

2. INCIDENCE OF ATYPICAL PRESSOR RESPONSES. Only one of the normal subjects exhibited exertional hypotension (Table 1). Patients with increased volume loads on the heart due to patent ductus arteriosus, atrial septal defect, mitral regurgitation, or aortic reguritation occasionally exhibited an inadequate increase in systolic pressure during exercise in from 11 to 20% of the cases studied. The incidence was somewhat higher in patients with external pressure loads due to either coarctation of the aorta or essential hypertension. Patients with an intracardiac pressure gradient due to stenosis of either the mitral or aortic valve exhibited exertional hypotension in over 40% of the cases studied. These observations indicate that exertional hypotension is not specific for any single pathological lesion of the cardiovascular system.

Although a rebound in systolic pressure during recovery was not observed either in normal subjects or in patients with patent ductus arteriosus, it occurred in from 13 to 44% of patients in all other groups under investigation (Table 1). The highest incidence was found with mitral stenosis, mitral re-

gurgitation and aortic stenosis. Curiously, the incidence was much lower in patients with aortic regurgitation.

Neither the normal subjects, nor any of the patients with patent ductus arteriosus, atrial septal defect or coarctation of the aorta exhibited both exertional hypotension and recovery rebound, but from 26 to 33% of the patients with stenosis of either the mitral or aortic valve manifested both unusual pressor responses to exercise (Table 1).

TABLE 1.—ATYPICAL PRESSOR RESPONSES TO UPRIGHT POSTURE AND EXERCISE

Group	*Number*	*Exertional Hypotension* %	*Recovery Rebound* %	*Both* %
Normal Subjects	16	6	0	0
Patients with Volume Loads				
Atrial Septal Defects	14	17	17	0
Patent Ductus Arteriosus	18	11	0	0
Mitral Regurgitation*	25	16	40	12
Aortic Regurgitation*	15	20	13	13
Patients with Pressure Loads				
Coarctation of Aorta	9	22	22	0
Hypertensive Disease	25	28	20	12
Patients with Intra-cardiac Pressure Gradients				
Mitral Stenosis*	45	44	44	26
Aortic Stenosis*	18	44	39	33

*Patients with valvular heart disease are classified according to predominant valvular lesion.

3. ATYPICAL PRESSOR RESPONSES IN MITRAL VALVULAR DISEASE. Preoperatively, the average systolic pressure during standing and walking was lower in patients with stenosis of either the mitral or aortic valve than it was in normal subjects* (Fig. 2). Patients with mitral stenosis had higher average systolic pressures while sitting after exercise than did patients with aortic stenosis. There was little difference in mean systolic pressure during walking in patients with mitral regurgitation, when compared with values for normal subjects (Fig. 3). Only 19 (76%) of the patients with mitral regurgitation and 25 (56%) of the patients with mitral stenosis were able to walk for 10 minutes at this rate of energy expenditure. It should be noted that patients with predominantly mitral regurgitation showed a minor fall in systolic pressure toward the end of exercise, followed by a recovery rebound which slightly exceeded the pressure levels of normal subjects (Fig. 3).

In order to evaluate the relationship between recovery rebound and exertional hypotension preoperatively, patients with mitral stenosis were subdivided into 3 groups of 15 patients each as follows:

Group I Systolic rebound greater than 24 mm. Hg

*These differences in patients with mitral stenosis, which ranged from 17 to 23 mm. Hg below the normal mean, were significant ($p<.01$) in the sixth, ninth and tenth minutes of exercise. Differences in the third minute of exercise ($p = .014$) and the first minute of recovery ($p = .045$) were not considered significant. Since there was no significant difference in diastolic pressure, these data were disregarded.

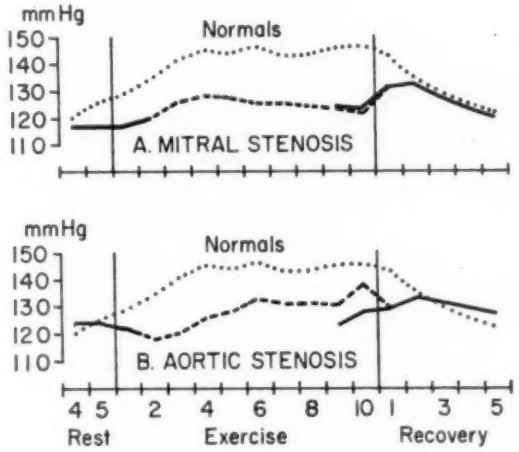


Fig. 2.—Average changes in systolic pressure with exercise in patients with either mitral stenosis or aortic stenosis. Inasmuch as all patients were unable to continue this exertion for 10 minutes, the broken lines indicate the average values for those patients who were able to walk for more than one, but less than 10 minutes. The interrupted solid line at the end of the exercise period represents the average value for the last 2 minutes of exercise for all patients regardless of how long they actually walked. Data in Figs. 3, 4 and 5 are grouped similarly.

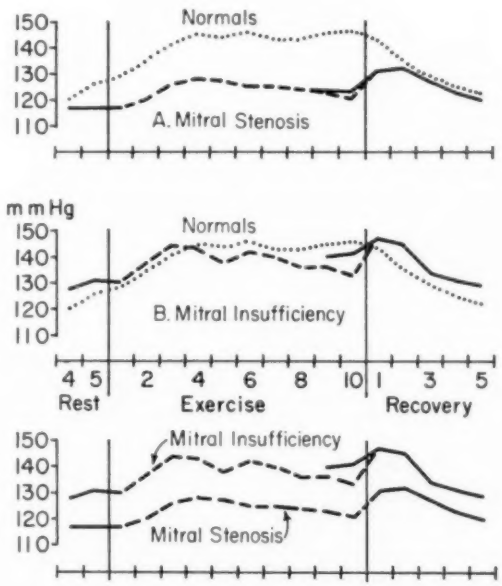


Fig. 3.—Comparative changes in average systolic pressure with exercise in patients with either mitral stenosis or mitral regurgitation.

Group II Systolic rebound from 4 to 24 mm. Hg

Group III Systolic rebound less than 4 mm. Hg

Patients in Group I exhibited hypotension and tachycardia during exercise, and a slightly more rapid deceleration of heart rate in recovery (Fig. 4). Eight of these patients who had atrial fibrillation showed higher systolic pressures and faster rates during exercise than the others who had a sinus mechtolic pressures during exercise and recovery which were close to the mean values for normal subjects (Fig. 5). On the other hand, those who obtained a "poor" result from surgery showed less change with respect to systolic pressure during exercise. Both groups still showed a tendency toward recovery rebound, however.

Discussion. Fraser and Chapman[6] recorded intraarterial blood pressure in 41 normal subjects walking on a

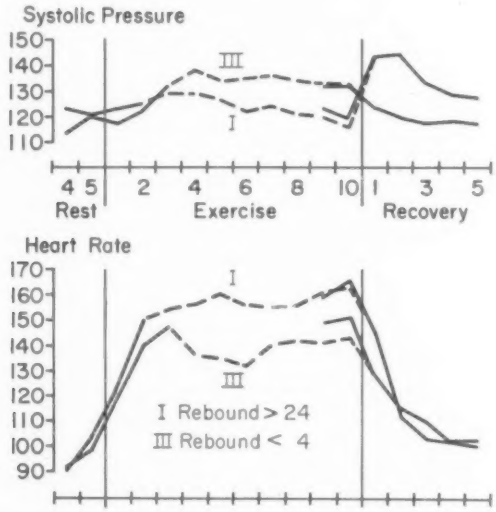


Fig. 4.—Average systolic pressure and heart rate during exercise in patients with mitral stenosis selected according to magnitude of rebound of systolic pressure observed during recovery. I = average values for patients with rebound greater than 24 mm. Hg, III = average values for patients with rebound less than 4 mm. Hg.

anism. The pressures recorded in Group III patients did not vary significantly from those of normal subjects, whereas those for patients in Group II were intermediate with respect to magnitude of change during exercise.

At the time of maximal postoperative improvement (average 8.4 months, range 1 to 29 months), patients who obtained a "good" result from mitral commissurotomy exhibited mean systreadmill at 3.0 mph on a 5% grade, and found that the mean systolic pressure increased 15 mm. Hg (12%), while the mean diastolic pressure decreased 7 mm. Hg. Although the change in systolic pressure was comparable to the 19 mm. Hg (15%) increment observed in normal subjects in the present study, the change in diastolic pressure was different. Possibly the difference in work-load accounts for this disparity in diastolic pressures. Changes during

recovery period were nearly similar in the two studies.

In the present study, both exertional hypotension and recovery rebound of systolic pressure were frequently observed in patients with stenosis of either the mitral or aortic valve. Although recovery rebound was often seen in patients with mitral regurgitation, the incidence of exertional hypotension was low. The mechanisms of these abnormalities are under study. The infrequent occurrence of exertional hypotension after successful mitral commissurotomy suggests that valvular stenosis limits cardiac output during effort.

Studies of cardiac output during exercise in the supine posture in patients with aortic or mitral stenosis often show an inability on the part of such patients either to maintain or to increase stroke output (Donald, Bishop and Wade[5], Gorlin *et al.*[7], Harvey[8] and Judson *et al.*[9]). Cardiac output could be increased only by acceleration of heart rate. The response of arterial pressure to effort is also affected by changes in systemic vascular resistance due to vasodilatation in skeletal muscles during exercise. It is of interest that only one patient with severe mitral stenosis exhibited a fall in systemic pressure during exercise, followed by a rebound, when studied in the horizontal posture by Donald, Bishop and Wade[5]. Chapman and Fraser[4] also observed a fall in mean arterial pressure, in spite of an increase in an already high cardiac index, in 1 out of 9 patients with a healed myocardial infarct who were studied during walking on a treadmill. More recently, studies of intraarterial pressure, described elsewhere, have shown a fall in mean pressure during walking, in

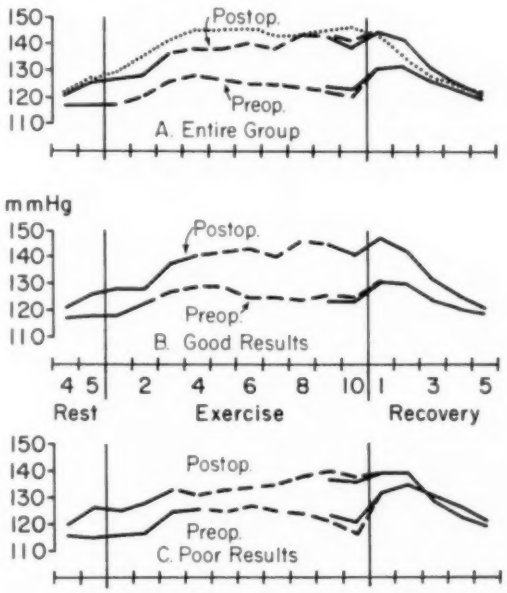


Fig. 5.—Effects of mitral commissurotomy on average systolic pressure during exercise in entire group of patients and those with either "good" results or "poor" results.

spite of an increase in cardiac index, in 4 out of 13 patients with cardiovascular diseases (Bruce, Andrus and Fuller[2]). Thus it is apparent that exertional hypotension probably represents an inappropriate circulatory adaptation to exertion in the upright posture, due to a marked fall in peripheral resistance from vasodilatation in skeletal muscles, and a quantitatively insufficient increase in cardiac output. It should not necessarily be interpreted as a sign of a "fixed cardiac output," but rather as a sign of insufficient peripheral vascular resistance for the available cardiac output. Since exertional hypotension can occur in a normal subject with inappropriate vasomotor regulation, heart disease is not necessarily a prerequisite to its manifestation. It is observed more frequently, however, in patients with an intracardiac pressure gradient due to valvular stenosis.

Summary and Conclusions. 1. Changes in systolic blood pressure to a standard test of exercise tolerance which utilized walking have been analyzed in normal subjects and in patients with various types of heart diseases. Exertional hypotension and recovery rebound were found occasionally in cardiac patients with volume loads and frequently in patients with stenosis of either the aortic or mitral valve.

2. In patients with mitral regurgitation, exertional hypotension was less common, although recovery rebound was just as frequent as it was in mitral stenosis.

3. Following mitral commissurotomy, mean systolic pressure during exercise returned toward normal in those patients who obtained a good result.

4. Inappropriate changes in systemic vascular resistance in relation to available cardiac output, are suggested as the probable mechanisms for the atypical pressor responses during exertion in the upright posture.

REFERENCES

1. **Bruce, R. A.:** Mod. Conc. Cardiovasc. Dis., **25**, 321, 1956.
2. **Bruce, R. A., Andrus, W. W.,** and **Fuller, T. J.:** Exertional Hypotension in Cardiac Patients. To be published, 1958.
3. **Bruce, R. A.,** and **Rodgers, D. L.:** Am. J. Med., **15**, 35, 1953.
4. **Chapman, C. B.,** and **Fraser, R. S.:** Circulation, **9**, 347, 1954.
5. **Donald, K. W., Bishop, J. M., Wade, O. L.:** J. Clin. Invest., **33**, 1146, 1954.
6. **Fraser, R. S.,** and **Chapman, C. B.:** Circulation, **9**, 193, 1954.
7. **Gorlin, R., McMillan, I. K. R., Medd, W. E., Matthews, M. B.,** and **Daley, R.:** Am. J. Med., **18**, 855, 1955.
8. **Harvey, R. M.:** *In* International Symposium on Cardiovascular Diseases, Henry Ford Hospital. Philadelphia: W. B. Saunders Co., p. 146, 1955.
9. **Judson, W. E., Hatcher, J. D., Hollander, W.,** and **Halperin, M. H.:** J. Clin. Invest., **34**, 1297, 1955.

(Interlingua on page 146)

THE EFFECT OF HEPARIN UPON THE TOTAL OXYGEN CONSUMPTION OF ATHEROSCLEROTIC INDIVIDUALS*

By H. Engelberg, M.D.
BEVERLY HILLS, CALIFORNIA

In a previous report[10] increases in forearm arteriovenous oxygen differences in a majority of atherosclerotic patients were noted after the injection of heparin. This work had been stimulated by a prior observation[7] of improvement in the ballistocardiograms of some patients with angina several hours after heparin was administered intravenously. However, since the forearm data were not correlated with simultaneous determinations of blood flow, a true increase in tissue oxygen consumption after heparin was not completely established. Accordingly, in the present study, total oxygen consumption was measured in atherosclerotic individuals before and after heparin, thus eliminating the need for determinations of blood flow. Data were also obtained of the rate of oxygen uptake by erythrocytes after heparin. These will be presented in a separate report.

Procedure and Methods. A total of 46 subjects were studied, all of whom had sustained a myocardial infarction in the past, but not in the preceding 6 months. The age range was from 42 to 81 years. No individuals were used who were in obvious congestive failure. The same room was used throughout the investigation and room temperature was maintained at 26° ± 1°. The patients did not eat after the evening meal and came to the hospital without breakfast the following morning. If they had slept poorly, had an elevated temperature, or were obviously disturbed, they were sent home. After resting for one-half hour the pulse and blood pressure were recorded, and several 3-minute samples of expired air were collected in Douglas bags when quiet breathing had been attained after adjustment of the mouthpiece and nasal clamp. In several instances the subjects were quite upset by the collection procedure and no further studies were performed with these individuals. Directly following the collection of the initial air samples, blood was drawn for clotting time and optical density determinations, and 100 mg. of heparin (100 mg. per ml.) was given intravenously. Samples of expired air were obtained 5 to 8 minutes after the injection, and the pulse, blood pressure and blood samples again taken. At this point the patients were allowed to sit up or walk around for the next one and one-half hours, and they then rested in bed for one-half hour before the third sample of expired air was collected. After the blood pressure and pulse were recorded, the final blood sample was obtained for chemical, optical density and clotting time determinations. In 12 individuals the studies were repeated after saline placebo injections, and in 7 basal oxygen consumption was measured after therapeutic levels of hypoprothrombinemia had been attained by 3 to 6 days of Dicumarol therapy.

Expired air samples were analyzed for oxygen and carbon dioxide content in a Haldane gas analysis apparatus, and volume was measured with a wet-test gas meter. Oxygen consumption was calculated from these data.

The Lee-White clotting times were determined at room temperature by means of a two-tube technique. In this study we were concerned only with gross demonstrations of anticoagulant activity. Serum optical density was measured in a Coleman Jr. spectrophotometer at 700 mμ. The optical density was observed simply to indicate that post-heparin lipemia clearing activity had occurred.

Results. The basal oxygen consumptions and the respiratory quotients be-

*This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract #AF 18 (600)–1703. Reproduction in whole or in part is permitted for any purpose of the United States Government.

TABLE 1.—TOTAL OXYGEN CONSUMPTION AND RESPIRATORY QUOTIENT IN 46 ATHEROSCLEROTIC PATIENTS BEFORE AND AFTER HEPARIN

						After 100 mg. Heparin I.V.				
				Control		*5–10 min.*		*2 hours*		
Patient	*Age*	*Weight*	*Sex*	O_2*	*RQ*	O_2	*RQ*	O_2	*RQ*	*Change in* O_2
R.B.	65	107	F	79	.70	60	.83	97	1.0	+23%
S.B.	64	174	M	215	.87			200	.96	− 7%
S.G.	62	175	M	197				235		+19%
H.G.	58	144	M	193	.75	243	.68	227	.69	+18%
B.W.	57	181	M	196	.84			194	1.0	—
D.B.	71	145	M	189	.80	183	.79	159	.75	−16%
A.A.	72	158	M	227	.70	237	.71	232	.76	—
M.W.	56	141	M	217	.91	195	.76	281	.83	+29%
M.T.	66	180	F	194	.85	196	.76	211	.70	+ 9%
Z.T.	52	165	M	175	1.0	204	.81	253	.71	+45%
R.K.	59	172	F	251	.70	252	.76	256	.76	—
L.C.	81	142	M	157	.78	174	.79	176	.78	+12%
V.S.	61	160	F	175	.77	194	.74	181	.77	—
S.B.	70	185	M	234	.79	247	.84	228	.75	—
F.R.	66	135	F	152	.85			146	.83	—
J.C.	64	157	M	247	.70	313	.88	316	.78	+28%
J.G.	72	182	M	320	.70	275	.89	412	.70	+29%
I.E.	53	135	M	229	.69			225	.71	—
B.Y.	42	142	M	249	.70	251	.71	233	.71	− 6%
D.J.	76	121	F	128	.73	124	.70	140	.74	+ 9%
I.G.	47	152	F	150	.71	138	.70	169	.71	+13%
L.G.	72	135	M	189	.76	224	.95	321	.70	+70%
F.W.	65	128	F	178	.76			191	.70	+ 7%
D.M.	69	127	M	228	.75	234	.76	223	.71	—
A.Z.	70	193	M	257	.70	257	.70	254	.70	—
H.U.	69	140	M	79	.84	171	.96	153	1.0	+94%
E.M.	61	169	M	185	.96	182	.91	200	1.0	+ 8%
L.C.	74	138	M	122	.90	123	.74	121	.96	—
B.E.	65	174	M	223	1.0	260	.88	230	.90	—
B.M.	57	96	F	63	.81	97	1.0	112	1.0	+77%
H.W.	66	141	M	91	1.0	90	1.0	92	1.0	—
A.R.	67	161	M	96	1.0	136	1.0	107	1.0	+11%
R.G.	72	107	F	98	1.0	93	1.0	125	.80	+27%
H.L.	73	119	F	95	1.0	85	1.0	121	.93	+26%
H.D.	52	170	M	262	.83	248	.87	252	.91	—
A.R.	59	126	F	227	.70	212	.84	265	.71	+12%
M.S.	62	150	F	164	.76	176	.98	142	1.0	−13%
G.B.	44	170	M	217	.79	223	.81	266	.71	+23%
F.W.	56	170	F	179	.92	167	1.0	276	.70	+54%
M.S.	49	132	M	255	.87	250	.87	240	.89	− 6%
S.R.	60	170	F	219	.69	206	.70	199	.69	− 9%
L.P.	68	180	M	333	.70	362	.70	440	.70	+32%
J.C.	70	146	M	176	.70	176	.70	195	.71	+11%
R.H.	62	121	F	138	1.0	137	1.0	114	1.0	−17%
S.N.	50	150	M	248	.89	270	.92	266	.82	+ 7%
M.S.	66	116	M	207	.75	212	.79	226	.76	+ 9%

*in ml. per minute

fore and after 100 mg. heparin intravenously are presented in Table 1. The control values in most instances are the averages of two separate 3-minute samples of expired air. In 5 patients no analysis was made in the first 5 to 10 minutes after heparin. Although the data are not shown in the table, there was marked prolongation of the clotting time in both post-heparin samples, usually of greater degree in the 10-minute one. Decreases in plasma optical density of varying degree were also found after heparin. In the last column of Table 1, the per cent change in oxygen consumption is calculated upon the basis of the control and 2-hour figures.

TABLE 2.—SUMMARY OF DATA IN 46 PATIENTS AFTER 100 MG. I.V. HEPARIN

Oxygen Consumption After Heparin	*Number of Individuals*	*Average Change*	*Initial Oxygen Consumption°*
Increased	20	32.7%	174
Decreased	3	15.3%	164
Unchanged	23		205

°In ml./minute

The results are summarized in Table 2. Changes in oxygen consumption less than 10% are not included since minor fluctuations occur spontaneously in duplicate samples of expired air. In 23 individuals there was no change, in 3 there was a decrease averaging 15.3%, and in 20 there was an increase in oxygen consumption averaging 32.7%. The difference between the number showing increase vs. those having a decrease in oxygen consumption after heparin (20:3) is statistically significant (chi square test). It is apparent from the figures in the final column of Table 2 that the initial oxygen consumption of the subjects who had an increased O_2 uptake after heparin was lower than those in whom no change took place. The changes in RQ are not summarized in Table 2. An inspection of the data in Table 1 reveals that the respiratory quotient in these fasting subjects was increased, decreased or unchanged after heparin.

TABLE 3.—STATISTICAL ANALYSIS OF DATA. PATIENTS PLACED IN 5 GROUPS ACCORDING TO CONTROL OXYGEN CONSUMPTION

Initial O_2 Consumption in ml./min.	*Standard Deviation*	*No. of Subjects*	*O_2 Consumption After Heparin*		
			Significant Increase		*Significant Decrease*
			$p = .05$	*$p = .01$*	*$p = .05$*
60–100	11.8	7	2	2	0
101–150	10.5	4	0	0	1
151–200	13.4	15	2	3	1
201–250	12.5	14	0	4	0
over 251	33.5	6	0	2	0

A statistical analysis of the data is presented in Table 3. The 46 patients were divided into 5 groups according to their initial oxygen consumption and the standard deviation determined for each group. There were 4 patients who had a probably significant increase of oxygen consumption after heparin ($p = .05$) and in 11 the increase was definitely signifiant ($p = .01$). In 2 individuals there was a crease was definitely significant ($p = .05$) but no definitely significant decrease occurred.

TABLE 4.—TOTAL OXYGEN CONSUMPTION AFTER HEPARIN, AFTER SALINE PLACEBO INTRAVENOUSLY, AND AFTER ORAL ANTICOAGULANT

		Oxygen Consumption ml./min.				
			After I.V.			
Patient	*Intravenous*	*Control*	*5–10′*	*2 hours*	*Change in O_2*	*Dicumarol 1 week*
	Heparin	79	60	97	+23%	
R.B.	Saline	83	78	82	—	82
	Heparin	175	204	253	+45%	
Z.T.	Saline	202	184	172	−15%	202
	Heparin	247	313	316	+28%	
J.C.	Saline	260	278	262	—	251
	Heparin	320	275	412	+29%	
J.G.	Saline	290	280	274	—	284
	Heparin	189	224	321	+70%	
L.G.	Saline	206	186	202	—	210
	Heparin	79	171	153	+94%	
H.U.	Saline	94	106	127	+35%	110
	Heparin	63	97	112	+77%	
B.M.	Saline	71	82	80	+13%	78
	Heparin	98	93	125	+27%	
R.G.	Saline	92	90	86	—	
	Heparin	95	85	121	+26%	
H.L.	Saline	104	92	88	—	
	Heparin	179	167	276	+54%	
F.W.	Saline	160	171	158	—	
	Heparin	333	362	440	+32%	
L.P.	Saline	320	352	348	+ 9%	
	Heparin	248	270	266	+ 7%	
S.N.	Saline	224	210	213	− 4%	

A comparison is presented in Table 4 of the heparin and placebo data obtained in 12 individuals in whom increases in oxygen consumption were found after heparin. It is clear that the results after placebos were not comparable to those obtained after heparin. The basal total oxygen consumption of 7 of the 12 subjects was also determined after 3 to 6 days of Dicumarol therapy when therapeutic levels of prothrombin depression had been attained. These figures are shown in the final column of Table 4 and illustrate that the oral anticoagulants, which do not decrease serum low density lipoproteins as heparin does, do not elevate oxygen consumption. There were no marked changes in the blood pressure, pulse rate, or temperature after the injection of heparin.

Discussion. The results of the present study, showing an average increase of total basal oxygen consumption after heparin of 32.7% in 20 of 46 atherosclerotic patients, closely paralled those previously reported after measuring forearm arteriovenous oxygen

differences (Engelberg and Kuhn[10]). In the latter, the possibility of changes in blood flow were not ruled out as a factor contributing to the increased A–V oxygen differences after heparin. However, the question of blood flow is of no concern when total body oxygen consumption is determined. The level of tissue metabolism is the major factor involved.

Since these observations of a true metabolic increase after heparin are surprising, it is of interest to probe the mechanisms possibly involved. The placebo data argue strongly against the possibility that the results were due to an emotional reaction. Obviously nervous or uncooperative patients were not studied. Furthermore, it was probable that if apprehension contributed at all to an increase in ventilation, it was less of a factor after the subjects had become familiar with the experimental procedure, namely in the post-heparin samples. Basal metabolism is, of course, increased by the thyroid hormone. However, there is no known effect of heparin upon the thyroid gland, and there was no increase of pulse rate, blood pressure or temperature in our patients. In some individuals the increase in oxygen consumption began within 5 to 10 minutes after the heparin was injected, a very short time interval for the thyroid hormone to act. Several facts indicate that the anticoagulant action of heparin was not responsible for the observed effects. In many of the subjects the oxygen consumption 5 to 10 minutes after heparin was not above control values whereas it was elevated 2 hours later although clotting times were most prolonged shortly after the injection. Also there was no comparable rise in oxygen uptake with the oral anticoagulants. There is no known direct stimulation of cellular metabolism by heparin *in vivo* as has been demonstrated with insulin and diabetic muscle (Hall[19]). In one observation[9] there was no increase of oxygen uptake by the mitochondria of sea urchin eggs when heparin was added to the surrounding medium.

In 1943, Hahn[18] found that heparin abolished alimentary lipemia. The lipid alterations involved in this "clearing" or reduction in turbidity of lipemic plasma were clarified by the observation from Gofman's group[15] that there is a rapid and profound alteration in the blood lipoprotein spectrum following the administration of heparin. When it is injected into humans or experimental animals whose plasmas contain elevated levels of chylomicrons or of low density or beta lipoproteins, these components quickly disappear from the blood. Subsequent investigation (Nichols *et al.*[25]) has disclosed that a true lipolysis of neutral fat-containing lipoproteins occurs with a splitting off of free fatty acids and glycerol, and that this process is associated with a rapid removal of fat from the blood stream (Grossman[16]). However, this increased rate of transfer of fat from the plasma to the tissues does not increase *per se* the oxygen consumption of the organism. The fat is merely available for storage or breakdown depending upon energy demand. There is no evidence or rationale which suggests that the delivery of fatty acids to the tissues stimulates metabolism.

It has been repeatedly shown that the serum lipid elevation of individuals with atherosclerotic disease as compared to matched "normal" controls consists of an absolute increase in the level of the low density or beta lipoprotein fraction (Barr, Russ and Eder[1] and Gofman *et al.*[14]). Thus atherosclerotic patients have a high concentration of those particular macromolecular particles which rapidly disappear

from the blood after heparin is given. In our earlier study[10] several observations indicated that the increase in arteriovenous oxygen difference roughly paralleled the decrease in the larger low-density lipoproteins. We may now consider how these macromolecular serum lipoproteins might interfere with tissue oxygen uptake. Although admittedly speculative the mechanisms which will be discussed are in keeping with known physiological and biochemical observations.

One of the simplest ways in which circulating lipids may prevent optimal cellular function is by interference with normal carbohydrate metabolism. It has been found that the sera of diabetic rats produce an insulin-reversible inhibition of glucose uptake by the diaphragm *in vitro* (Bornstein[2]). The inhibitor was associated with the beta lipoprotein fraction, and after the removal of these lipoproteins the diabetic rat sera were not inhibitory. The inhibitory lipoprotein was also obtained from the blood of a human subject. Thus, with the marked decrease in the low density lipoproteins after heparin, carbohydrate metabolism may proceed more normally and cellular function is improved. This may have been the chief reason for the increase in oxygen consumption in the 4 individuals (Table 1) in whom a fairly sharp rise in the respiratory quotient was found. However, since a decrease in the respiratory quotient was more frequent, it is unlikely that improved carbohydrate oxidative metabolism was primarily responsible in the majority of subjects.

Lipoproteins may also impair tissue function by the formation of films, either on the surface of blood cells or the intimal endothelium. Hueper noted that the inner wall of blood vessels was covered by a coat of polyvinyl alcohol and methylcellulose macromolecules[20, 21]. Surface films of high molecular weight dextrans on erythrocytes have been photographed (Thorsen and Hiat[28]). It has been shown (Pappenheimer, Renkin and Borrero[26]) and amply confirmed (Giebisch, Lanson and Pitts[13], Grotte[17], and Renkin[27]) that diffusion through capillary walls is a function of molecular size, that molecular sieving occurs, and that with increasing molecular size there is decreasing diffusion. The vascular walls under normal conditions are permeable to smaller molecules and almost impermeable to larger ones (Wilens and McCluskey[29]). Evans, using an aortic perfusion technique, has observed fatty material deposited upon the intima after several days of perfusion[11]. Wilens and McCluskey have noted that the neutral fat of chylous serum, which is carried predominantly as large chylomicra and lipomicra, was unable to enter into the walls of excised arteries[30]. Cullen and Swank[5] observed surface films on red blood cells after fat feeding. Thus, from a variety of observations, it is highly probable that it is predominantly the larger lipoproteins and chylomicra, precisely those which almost disappear following an adequate dose of heparin, which contribute to the accumulation of films. Because of their decreased ability to escape through the capillary walls they form fat sludges on the endothelium, clog capillary pores, and so mechanically interfere with the passage of other molecules across the capillary membrane. Further, lipid films, particularly if they are many layers deep, affect the solubility or diffusion constant of oxygen due to their property of combining with atmospheric oxygen (Davidson, Eggleton and Foggie[6]). Thus Martin and Hueper found a decreased rate of oxygen uptake by the erythrocytes of hypercholesterolemic rabbits[24]. In the earlier reports[7,10] it

was noted that when a ballistocardiographic improvement or an increased forearm A–V oxygen difference occurred after heparin, it was usually several days before the changes reverted. However, the lipoprotein levels after heparin returned to their initial values in a shorter period of time. Since the simple reaccumulation of circulating lipoproteins certainly occurs more quickly than the reformation of lipid films, the elimination of the latter was probably an important factor in the results observed.

Studies of the activity of proteins at interfaces, recently summarized (Fraser[12]), afford excellent evidence that large concentrations of circulating lipid macromolecules and lipid films can affect a host of metabolic reactions in another way. Proteins are adsorbed and spread at oil:water interfaces. They cannot always be easily displaced and may remain in strong association with the film molecules. The degree of packing of the lipid molecules in the film is important in the protein-lipid interactions. However, protein enzymes may also be bound by freely circulating lipid molecules. The micro-somal alkaline phosphatase and zanthine oxidase of cow's milk can be released with considerable increase in activity by various physical and chemical agents from the surface of the milk fat globules. Perhaps the most important result of protein adsorption at oil:water interfaces is the decrease in biological activity of most enzyme proteins which occurs as a result of surface denaturation. There is an unfolding of the secondary and tertiary structures of the protein which are essential for its function. Thus the inhibition of various enzymes by lipoproteins has been reported (Bornstein[3]). Also certain protein hormones are denatured on films and lose activity (Fraser[12]). It is, therefore, probable that as a result of the sharp decrease in the larger lipoproteins which occurs after heparin, many enzymatically controlled metabolic reactions proceed at a more normal rate.

Recent studies by Kuo and Joyner[22] have verified the relation of plasma lipemia to myocardial oxygenation. They observed that a slow intravenous injection of a sesame oil emulsion produced a drop in the oxygen tension and a decrease in the amplitude of myocardial contraction in a group of dogs in which a myocardial infarction had been produced by coronary ligation. Subsequently they demonstrated that postprandial lipemia induced attacks of angina at rest 3 to 5 hours after a fat meal in a small number of patients with severe coronary disease, with associated deterioration in the electrocardiogram and ballistocardiogram in some of the subjects. In a later publication[23] the same authors noted that post-lipemia angina was relieved within 10 minutes by intravenous heparin but not by saline placebos. They observed improved ballistocardiograms and electrocardiograms in some of these patients after heparin, thus substantiating our previous findings[7,10].

If a moderate number of hyperlipemic atherosclerotic individuals are truly in a state of low grade chronic tissue hypoxia, as both our control and post-heparin oxygen consumption data suggest, there are many possible implications. Lowered levels of oxidation could affect various metabolic functions adversely, play a role in tissue aging, perhaps even be a factor contributing to malignant degeneration by allowing cells to use more easily fermentative pathways for energy production in the presence of other carcinogenic stimuli. These are admittedly speculative thoughts at this time. However, there is one important area to which the findings presented in this

paper are more immediately pertinent, namely therapy in patients with acute myocardial infarction. At the present time a lowered caloric and fat intake is usually prescribed and heparin is administered for a few days followed by oral anticoagulants. The decreased fat intake may or may not lower lipid levels adequately, and is even less likely to cleanse intimal films. The oral anticoagulants do not increase oxygen consumption. Even slight deficiencies in oxygen supply have been shown to increase the likelihood of ectopic rhythms (Boyer and Murray[4]). There are also other beneficial actions of heparin, not possessed by the oral anticoagulants, which have recently been summarized (Engelberg[8]). The evidence of this study and others (Kuo and Joyner[23]) indicates the desirability of using heparin as the anticoagulant of choice in the therapy of acute coronary thrombosis for a longer period of time than a few days, perhaps for the entire anticoagulant period.

Summary. 1. Total basal oxygen consumptions and respiratory quotients were determined in 46 atherosclerotic patients before and after the injection of heparin.

2. In 20 individuals there was an average increase in oxygen consumption of 32.7%. In 3 there was an average decrease of 15.3%. In 23 there was no change after heparin.

3. There was no increase in oxygen consumption after saline placebos or oral anticoagulants.

4. The respiratory quotient showed no characteristic change although more frequently it fell after heparin.

5. Various possible mechanisms are discussed which indicate that the increase in oxygen consumption results from the lipemia clearing action of heparin.

REFERENCES

1. **Barr, D. P., Russ, E. M.,** and **Eder, H. A.:** Am. J. Med., **11**, 480, 1951.
2. **Bornstein, J.:** J. Biol. Chem., **205**, 513, 1953.
3. Idem: Biochem. and Biophys. Acta, **20**, 522, 1956.
4. **Boyer, S. H.,** and **Murray, J. F.:** Bull. Johns Hopkins Hosp., **100**, 141, 1957.
5. **Cullen, C. F.,** and **Swank, R. L.:** Circulation, **9**, 335, 1954.
6. **Davidson, D., Eggleton, P.,** and **Foggie, P.:** Quart. J. Exper. Physiol., **37**, 91, 1952.
7. **Engelberg, H.:** Am. J. Med. Sci., **224**, 487, 1952.
8. Idem: Ann. Int. Med., **44**, 466, 1956.
9. Idem: Unpublished data.
10. **Engelberg, H.,** and **Kuhn, R.:** Angiology, **7**, 73, 1956.
11. **Evans, S. M., Ihrig, H. K., Means, J. A., Zeit, W.,** and **Haushalter, E. R.:** Am. J. Clin. Path., **22**, 354, 1952.
12. **Fraser, M. J.:** J. Pharm. and Pharmacol., **9**, 497, 1957.
13. **Giebisch, G., Lanson, H. D.,** and **Pitts, R. F.:** Am. J. Physiol., **178**, 168, 1954.
14. **Gofman, J. W., Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H. A.,** and **Strisower, B.:** Circulation, **2**, 161, 1950.
15. **Graham, D. M., Lyon, T. P., Gofman, J. W., Jones, H. B., Yankley, A., Simonton, J.,** and **White, S.:** Ibid., **4**, 666, 1952.
16. **Grossman, M. I.:** J. Lab. & Clin. Med., **40**, 805, 1952.
17. **Grotte, G.:** Scandinav. J. Lab. & Clin. Med., **7**, 59, 1955.
18. **Hahn, P. F.:** Science, **98**, 19, 1943.
19. **Hall, S. C.:** Ibid., **119**, 813, 1954.
20. **Hueper, W. C.:** Arch. Path., **31**, 11, 1941.
21. Idem: Ibid., **33**, 1, 1942.
22. **Kuo, P. T.,** and **Joyner, C. R., Jr.:** J. Am. Med. Assn., **158**, 1008, 1955.
23. Iidem: Ibid., **163**, 727, 1957.
24. **Martin, G. S.,** and **Hueper, W. C.:** Proc. Soc. Exper. Biol. & Med., **49**, 452, 1942.

25. **Nichols, A. V., Freeman, N. K., Shore, B.,** and **Rubin, L.:** Circulation, **6,** 457, 1952.
26. **Pappenheimer, J. R., Renkin, E. M.,** and **Borrero, L. M.:** Am. J. Physiol., **167,** 13, 1951.
27. **Renkin, E. M.:** J. Gen. Physiol., **38,** 225, 1954.
28. **Thorsen, G.,** and **Hiat, H.:** Acta chir. Scandinav., Suppl. 154, 1950.
29. **Wilens, S. L.,** and **McCluskey, R. T.:** Am. J. Med. Sci., **224,** 450, 1952.
30. Iidem: Circulation Res., **2,** 175, 1954.

SUMMARIO IN INTERLINGUA

Le Effecto De Heparina Super Le Consumption Total De Oxygeno In Individuos Atherosclerotic

1. Le valores del total consumption basal de oxygeno e le quotientes respiratori esseva determinate in 46 patientes atherosclerotic ante e post le injection de heparina.

2. Le comparation del consumption de oxygeno ante e post heparina monstrava, coma effecto del droga, un augmento medie de 32,7% in 20 del patientes, un reduction medie de 15,3% in 3 del patientes, e nulle alteration in 23 del patientes.

3. Occurreva nulle augmento del consumption de oxygeno post le administration de solution salin como medication fictitie o post le ingestion oral de anticoagulantes.

4. Le quotiente respiratori non exhibiva un alteration characteristic sub le effecto de heparina. Tamen, su ascendita esseva plus frequente que su descendita post le administration del droga.

5. Es discutite varie mechanismos possibile. Il pare que le augmento del consumption de oxygeno resulta ab le activitate hypolipemic que es characteristic de heparina.

THE CLINICAL STUDY OF QUINIDINE POLYGALACTURONATE*

By Norman Shaftel, M.D.
ASSOCIATE ATTENDING PHYSICIAN, DIVISION I, KINGS COUNTY HOSPITAL MEDICAL CENTER; ASSISTANT ATTENDING PHYSICIAN, MAIMONIDES HOSPITAL, BROOKLYN, NEW YORK

AND

Alfred Halpern, Ph.D.
DIRECTOR, DEPARTMENT OF EXPERIMENTAL THERAPY, THE STUYVESANT POLYCLINIC NEW YORK, NEW YORK

Quinidine remains the "drug of choice" for the treatment of cardiac arrhythmias; however, limitations of the utilization of the conventional salts of this alkaloid have resulted because of the frequent gastrointestinal disturbances associated with its use (Shaftel and Halpern[34]). Because of these occurrences, both the therapeutic scope and clinical value of quinidine have been reduced to such degree that the investigation of new derivatives has become essential.

The present study concerns the clinical behavior of a new alkaloidal salt, quinidine polygalacturonate (Halpern, Shaftel and Montebovi[17]) which has been demonstrated to possess the full antiarrhythmic properties of quinidine (Halpern, Shaftel and Schwartz[18]).

While it has been established that nausea, vomiting and other intestinal symptoms may arise from central nervous system action (Ernstene and Lowis[14,15]) following large doses of quinidine, Gold[16] noted that the dosage of quinidine generally used in the treatment of arrhythmias, was rarely sufficient to cause vomiting by central action, while Kalmansohn and Sampson[21], investigating the relationship between plasma quinidine blood levels and toxic manifestations, discovered such wide variations in the quinidine blood levels of patients who developed gastrointestinal symptoms, that they concluded that alimentary upsets were due to local action on the intestinal tract. The preponderance of clinical data also indicates that these undesirable effects are most commonly due to a local irritative action rather than to systemic toxicity. It is this local effect that has constituted the principle reason for the withdrawal of the drug before a satisfactory therapeutic result could be achieved (Sokolow[35]).

In attempting to reduce the frequency of gastrointestinal disturbances caused by conventional oral quinidine therapy, various modifications in the modality of quinidine therapeusis were suggested. Berger[3] reported the successful use of intramuscular quinidine in restoring a sinus mechanism (without producing gastrointestinal disturbance) in a patient in whom oral quinidine had previously aggravated an existing ulcerative colitis. However, although it is acknowledged that nausea and vomiting may be avoided with parenteral quinidine, such administration exposes the patient to certain inherent dangers (Acierno and Gubner[1],

*The quinidine polygalacturonate used in this study was obtained through the courtesy of Dr. Martin C. Sampson, Medical Director, The G. F. Harvey Company, Saratoga Springs, New York, and is available as Cardioquin.

Blinder *et al.*[4], and Sokolow[37]) and from a practical standpoint, the parenteral route does not lend itself to the usual requirements of daily multiple dosage over prolonged or extended periods in ambulatory patients.

Another suggestion advanced to lessen the frequency of local quinidine irritation has been to lower the dosage. This generally does lessen the local irritative action but, by producing subtherapeutic blood levels, it simultaneously cancels the therapeutic value. Another modification, with which Russek[32] reported "striking success" concerned the use of a teaspoonful of paregoric given 15 minutes before the usual dose of quinidine. In several instances this regimen increased the gastrointestinal tolerance to quinidine sufficiently to permit continuance of the drug. Nonetheless, the continued and prolonged administration of an opium derivative would not appear to be an acceptable answer to the problem. Enteric coating of the quinidine tablet has also been suggested (Ditlefson and Knutsen[13]), but this delays absorption of the drug and thereby creates the additional difficulty of special dosage equilibrations, without appreciably affecting the problem.

QUINIDINE POLYGALACTURONATE

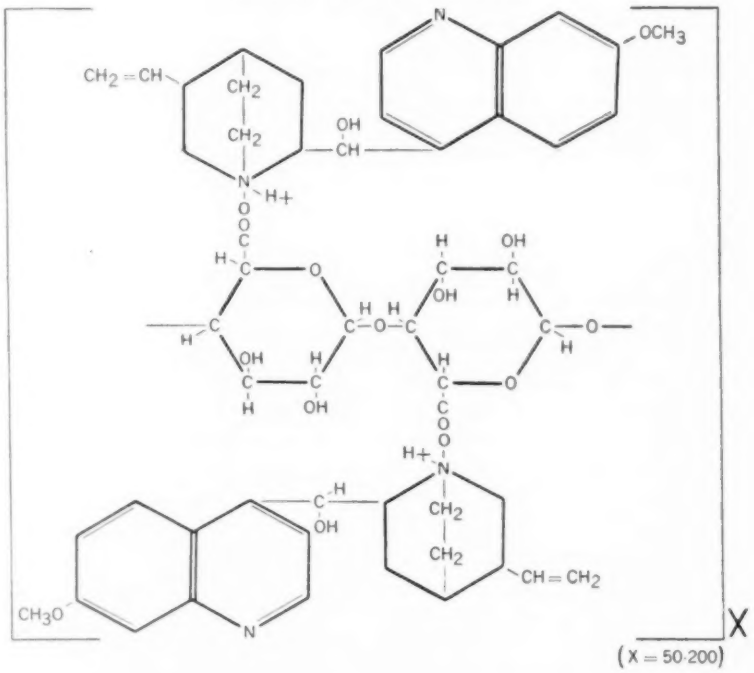


Fig. 1

RATIONALE OF QUINIDINE POLYGALACTURONATE. The theoretical basis for the development of quinidine polygalacturonate evolved from a desire to reduce the ionic shock to the gastrointestinal mucosa resulting from a flood

of irritating ions liberated during the rapid dissociation of the conventional inorganic quinidine salts.

By reacting the long-chain natural sugar derivative, polygalacturonic acid, with quinidine alkaloid, a slightly soluble, stable salt with a low dissociation constant, quinidine polygalacturonate (Fig. 1) was obtained (Halpern, Shaftel and Montebovi[17]). Since this new quinidine molecule is relatively insoluble, it releases its ions slowly, proportionate to its slow progressive dissociation and absorption. Thus, with quinidine polygalacturonate, ionic flooding of the gastrointestinal tract is avoided and a smoother counter-balanced system of quinidine availability, absorption and utilization results.

However, the factors of slow dissociation and absorption do not represent the only advantage of this new compound. The polygalacturonic acid moiety, which is derived from pectin, has been shown to possess special demulcent properties for the gastrointestinal tract (Kobren, Fellers and Esselson[23]). This fraction is not absorbed (Kertesz[22]) and acts through colloidal adsorptive (Malyoth[28]) and mucin sparing properties (Manville[29]) to inhibit mucosal irritation.

The versatility of polygalacturonic acid in allaying local intestinal mucosal irritation due to widely varied etiologies has been established (Crimm, Westra and Thompson[9], Malyoth[28], Manville[29], Manville *et al.*,[30] Tompkins and Howard[40] and Winters, Peters and Crook[44]). Polygalacturonates were reported to produce improvement in the symptoms of abdominal distress, distention, nausea and anorexia associated with enterocolitis (Crimm, Westra, and Thompson[9]) and the use of this agent to allay the diarrheas of bacillary dysentery was reported by Tompkins[40]. The detoxifying properties of the polygalacturonates were noted by Winters, Peters and Crook[44] who described the protective properties of the material against peptic ulcer induction by cinchophen. Manville and associates[30] studied the detoxification of lead and arsenic by polygalacturonates and reported striking protective effects. For these reasons, clinical use of the colloidal polygalacturonate in place of the strongly acid sulfate or hydrochloride ions of the conventional quinidine salts was considered to be of potential value in lowering the incidence and degree of gastrointestinal irritation which is frequently encountered during quinidin therapy.

PHARMACOLOGY OF QUINIDINE POLYGALACTURONATE. The pharmacology of quinidine has been exhaustively explored by many investigators (Dawes[10]). The essential pharmacodynamic effects of quinidine are exerted on the heart muscle and produce a depression, mainly in the atria. This is manifested by a depression of excitability, a slowing of conduction, suppression of idiopathic rhythm and by a diminution of vagal tone. In the electrocardiogram an increase of the refractory period is suggested by a prolongation of the PR interval as reported by Lewis and associates[26]. However, Gold and Kwit[25] reported no change or even a shortening of the PR interval. The effect on the heart rate of dogs with normal sinus mechanism has been variously described by investigators as increased (Kwit and Gold[25]), decreased (Sollmann[38]) or unchanged (Cohn and Levy[8]). In atrial fibrillation Lewis *et al.*[26] reported that while the atrial rate was slowed, the ventricular rate increased.

The acute oral toxicity of quinidine polygalacturonate was studied (Halpern, Shaftel and Schwartz[18]) in rats and mice. The method of Miller and Tainter[31] was used to compute the

LD_{50} and this was found to be 3200 ± 350 mg. per kg. body weight (slope factor = 3100 mg. per kg.) for the rat and 2680 ± 210 mg. per kg. body weight (slope factor =1840 mg. per kg.) for the mouse, based upon a 14-day observation period. The oral LD_{50} for quinidine sulfate is reported to be 593.1 ± 83 mg. per kg. for the mouse (Calesnick, Smith and Beutner[6]).

The effects of quinidine polygalacturonate were noted to be qualitatively identical to those of quinidine sulfate, but because of the slower dissociation and absorption of the former, the time-effect relationship was different in the dog (Halpern, Shaftel and Schwartz[18]). At a dosage level of 100 mg. per kg. quinidine base equivalents of both compounds to dogs, characteristic changes of the electrocardiogram were noted to begin at 1 to 2 hours and often reached peak effects between 4 to 5 hours after administration of the poygalacturonate. The electrocardiographic effects, however, were identical to those obtained with equivalent dosages of quinidine sulfate, indicating that the basic pharmacology of quinidine with respect to the heart, was not altered by substituting the polygalacturonate moiety for the sulfate ion[18].

In view of the above properties of quinidine polygalacturonate, it was considered important to study the clinical behavior of this drug in man. The objectives of this investigation were to study (a) the oral absorption and resultant blood levels of quinidine polygalacturonate, (b) the effects of the new agent on the electrocardiogram, (c) the antiarrhythmic properties of the drug and (d) the extent of local irritative effects on the gastrointestinal tract.

Methods and Materials. The absorption of quinidine polygalacturonate was investigated in both dogs and humans. The compound was administered to fasted, mongrel dogs at a dosage level of 100 mg. per kg. (Quinidine base equivalent) and periodic, serial determinations of the quinidine blood levels carried out. Equivalent doses of quinidine sulfate were also administered in order to provide a basis for comparison.

Single doses of 0.2 gm. and 0.4 gm.*, (quinidine base equivalent) were administered to human subjects and the blood quinidine levels determined. The effect of a multiple dosage regimen on the absorption and fluctuation of the blood quinidine levels of the new compound was studied in man by administering 0.2 gm., q.i.d., and 0.4 gm., q.i.d., for one day and determining the blood levels during a 48-hour period. The method used to determine the quinidine blood levels was that described by Archer, Weitzman and Kay[2].

Electrocardiographic analysis of the effects of quinidine polygalacturonate on the heart was conducted simultaneously with the blood level determinations in both dog and man. In this way it was possible to relate the electrocardiographic data to those previously described for quinidine sulfate, thereby providing a frame of reference.

The electrocardiographic alterations produced by high, but not acutely toxic, dosage of the quinidine compounds (100 mg. per kg., quinidine base equivalent) were studied in the dog. The effects of the lower dosage levels of conventional therapeutic practice were studied in man utilizing frequent 12 lead electrocardiograms during therapy with the test compound. These were compared with the electrocardiographic effects obtained during equivalent quinidine sulfate therapy.

Quinidine polygalacturonate was studied for its therapeutic effects on arrhythmias in a series of 50 patients presenting classic indi-

*The designation of a dose of 0.2 gm. and 0.4 gm. represents that amount of quinidine polygalacturonate which is equivalent in quinidine base content to 0.2 gm. and 0.4 gm. of quinidine sulfate. The actual total weight of quinidine polygalacturonate represented by this 0.2 gm. and 0.4 gm. designation is 0.266 gm. and 0.532 gm. respectively. This method of dosage representation was adopted better to evaluate the results obtained because of the well known clinical activity of these widely utilized dosages of quinidine sulfate for the management of cardiac arrhythmias.

cations for quinidine therapy. Among the arrhythmias studied were atrial fibrillation (21 patients), atrial flutter (2 patients), paroxysmal atrial fibrillation (5 patients), paroxysmal atrial tachycardia (8 patients), premature ventricular contractions (9 patients), premature atrial contractions (4 patients) and premature contractions of multifocal origin (1 patient).

The underlying etiologies were atherosclerotic heart disease (21 patients), hypertensive heart disease (12 patients), rheumatic heart disease (13 patients) and of unknown origin (4 patients). The patients studied ranged in age from 14 to 80 years, and the group included 21 males and 29 females. The cardiac arrhythmia was present for one year or less in 24 of the series; 8 patients presented a history of 1 to 2 years' duration; in 14 patients it was present for from 2 to 5 years and in 4 patients for more than 5 years.

The diagnosis of the arrhythmias was confirmed in each case by electrocardiogram before the test drug was administered. When a rapid effect was desired, six grains (0.4 gm.) were administered every 2 hours for 5 doses. When there was no urgency, the patient was started on three or six grains (0.2 to 0.4 gm.), three or four times daily. When the desired response was not obtained, the dosage was increased by 0.2 gm. After converting the arrhythmia to a normal sinus mechanism, maintenance therapy was generally accomplished with three grains (0.2 gm.), once or twice daily although some patients required larger dosage.

The local gastrointestinal effects were evaluated subjectively by carefully questioning each of the patients for the presence of any symptomatology referable to the drug and objectively for evidence of vomiting and diarrhea. When the opportunity presented, patients who previously were unable to tolerate quinidine sulfate were given the test compound in order to comparatively evaluate the degree of local irritation.

Results. (a) ORAL ABSORPTION. The blood levels determined after quinidine polygalacturonate administration establish that the new compound was absorbed into the blood stream in a manner comparable to quinidine sulfate (Fig. 2). In fasted dogs fed 100 mg. per kg. (quinidine base equivalent) of both compounds, quinidine blood levels were observed within one-half hour. The peak values of the sulfate were achieved earlier than that of the galacturonate, (1 to 6 hours in contrast to 4 to 24 hours) with the sulfate peak slightly higher than that of the polygalacturonate. Blood quinidine levels approximating the peak values were attained within 2 to 4 hours with both compounds. While the peak value of quinidine sulfate declined rapidly, a plateau was observed after the administration of the polygalacturonate. Thus, the latter compound caused a more persistent and uniform blood concentration. It is of interest, in this connection, to note empirically the similarity between the curves produced by the polygalacturonate in the fasted dog and that of quinidine sulfate in the nonfasted dog. At 24 hours, appreciable blood quinidine levels persisted and a rather close conformity of behavior was observed between both compounds. The 24-hour quinidine sulfate level averaged 0.77 mg. per 100 ml. and the quinidine polygalacturonate average was 0.87 per 100 ml. Almost complete disappearance of both from the blood stream was observed after 48 hours.

Within therapeutic dosage range, the blood level patterns observed in man were roughly comparable to those observed in dogs receiving the high quantities. While there were rather broad individual differences as to the time the peak levels were achieved, these particular peak values were dramatically constant for each of the single doses administered.

The range of peak blood levels after a single dose of 0.2 gm. (quinidine base equivalent) (Fig. 3) was from 2.1 mg. per L. to 2.8 mg. per L. and after 0.4 gm. (quinidine base equivalent) (Fig. 4) from 3.2 to 4.2 mg. per L. In 50% of the small group receiving medication four times daily, the 24-hour level (approximately 12 hours

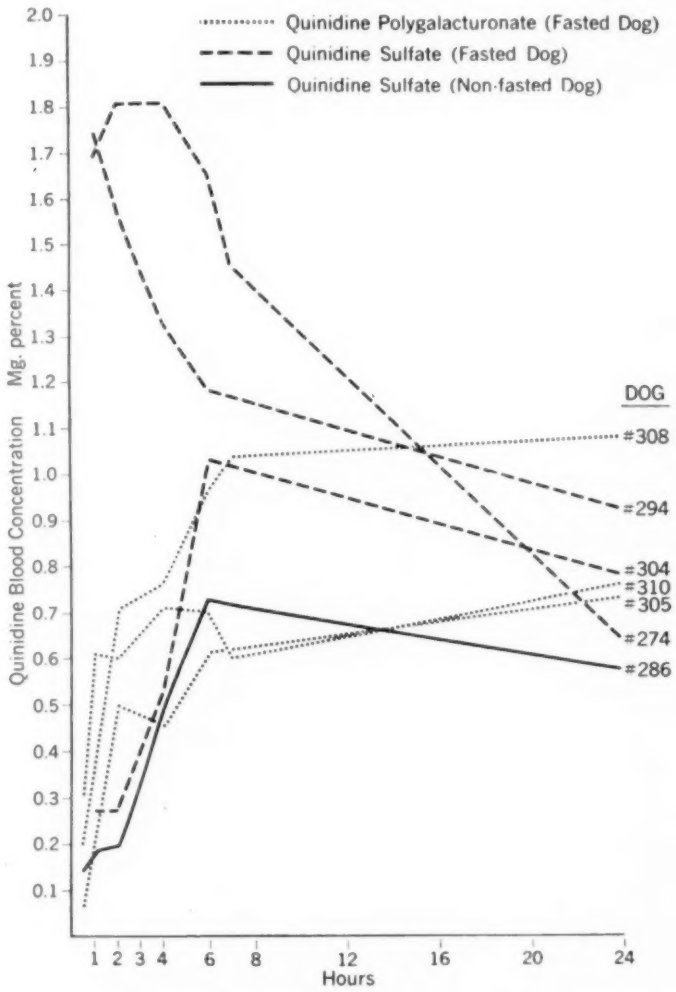


Fig. 2.—A comparison of the quinidine blood levels observed after the administration of equivalent doses (100 mg. quinidine base per kg.) of quinidine sulfate and quinidine polygalacturonate to dogs.

after the last dose) indicated a falling off of about 15 to 20% of the peak value (Fig. 5). At 48 hours only traces of quinidine were found in the blood.

Numerous studies of the quantitative aspects of quinidine therapy have been reported (Brown, Holzman and Creelman[5], Ditlefson[11], Linenthal, Ulick and Patterson[27] and Sampson, Foreman and Solomon[33]) in an effort to relate quinidine blood levels to both the cardiac effect and the toxic manifestations. A common point of emphasis of these investigations was the bizarre variation observed among the individual absorption patterns. For example, in a recent paper, Sokolow[36] noted as much as fivefold variation in serum quinidine

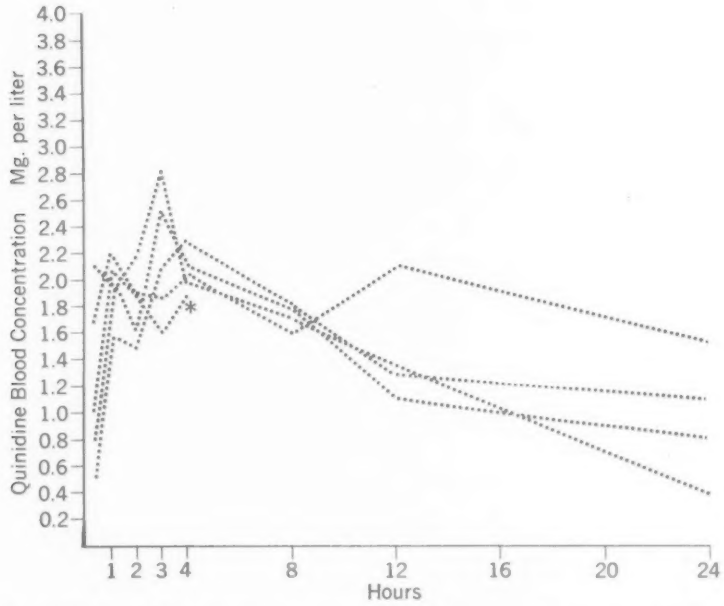


Fig. 3.—The quinidine blood levels determined after the administration of 0.266 gm. of quinidine polygalacturonate (equivalent to 0.2 gm. of quinidine sulfate) in man.

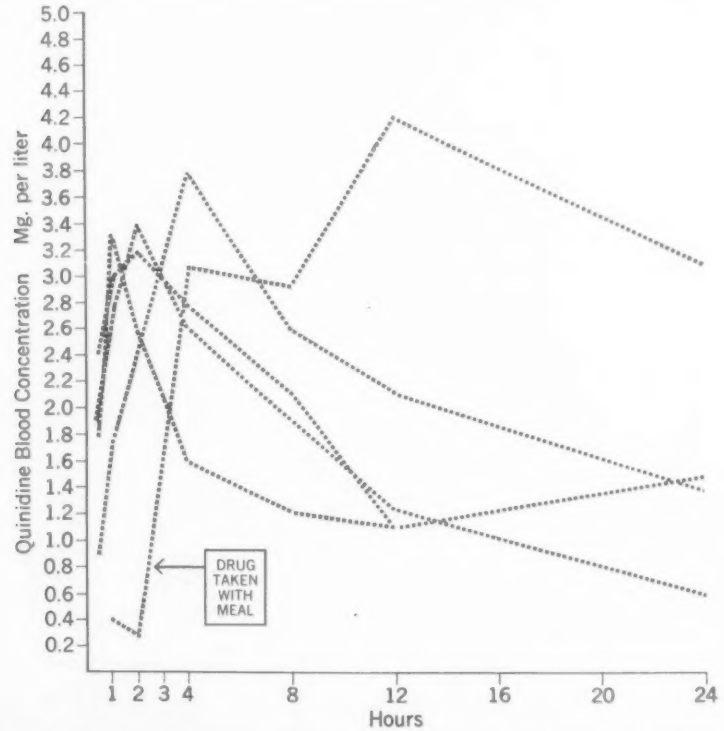


Fig. 4.—The quinidine blood levels determined after the administration of 0.532 gm. of quinidine polygalacturonate (equivalent to 0.4 gm. of quinidine sulfate) in man.

concentration on identical dosage. Similar observations have been made by other workers (Brown, Holzman and Creelman[5], Linenthal, Ulick and Patterson[27], Sampson, Foreman and Solomon[33], and Sokolow[36]) and the consensus is that quinidine absorption was found in the blood 7 minutes after injection (Weisman[42]). In cats only 5% of the injected dose could be determined in the blood 5 minutes after injection (Weiss[43]). When an essentially stable plasma level was obtained, the tissue level of the drug was ap-

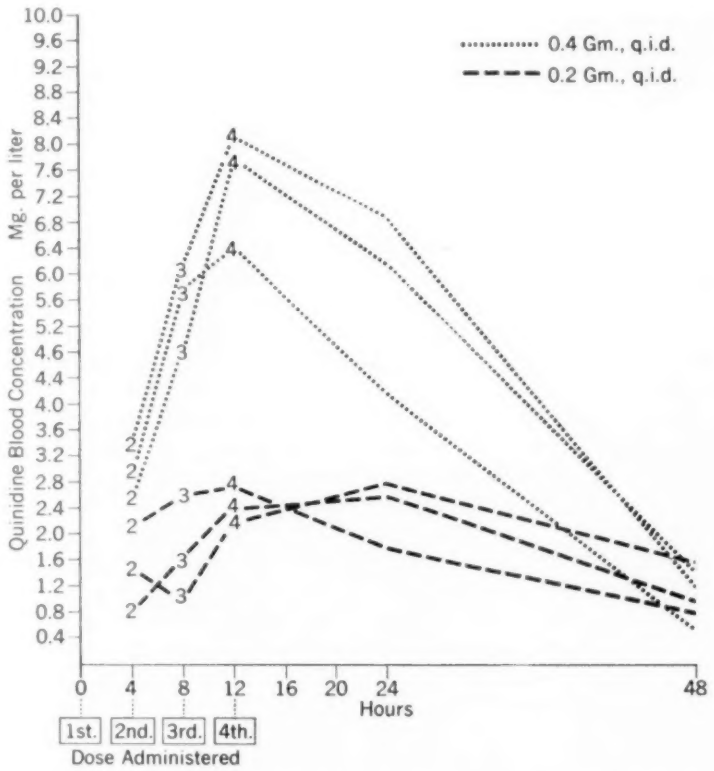


Fig. 5.—The blood quinidine levels determined after multiple dose administration of quinidine polygalacturonate in man. The dosage represented refers to equivalent doses of quinidine polygalacturonate to 0.2 gm. and 0.4 gm. of quinidine sulfate.

follows a pattern that is subject to gross individual difference.

A difficulty in evaluating the significance of quinidine blood levels, is that quinidine rapidly diffuses into the body organs from the blood stream. After intravenous injection of a dose of quinidine into dogs, less than 6% proximately ten to twenty times greater than that of the blood, with peak values found in glandular tissue and lungs (Hiatt and Quinn[19]). Of the muscular tissues of the dog, the head appears to have the greatest concentration, with the diaphragm and gastrocnemius muscle next in rank (Weisman[42]). The

parallel curves of the rise and fall of the tissue and plasma quinidine levels indicate a ready transfer from the tissue, as the blood level falls, with no significant time-lag in diffusion from the tissues (Hiatt and Quinn[19] and Wegria and Boyle[41]). It has also been shown (Yount and Rosenblum[45]) that the peak levels are achieved more quickly if the stomach is empty at the time of drug administration.

These factors may account, at least in part, for the gross individual variations observed in previous studies (Brown, Holzman and Creelman[5], Sokolow[36], Weisman[42] and Weiss and Hatcher[43]) and confirmed in the present study. However, in spite of the individual variations noted for the separate blood level curves determined in man, the constancy of the values resulting after quinidine polygalacturonate administration are of particular interest. The narrower range of peak values may be indicative of a more uniform absorption. This may be explained by the postulated controlled availability of the quinidine ion resulting from the slightly soluble and weakly dissociable compound[17]. The apparent sustained levels observed with the high dosage of the polygalacturonate administered to animals were not evident when the smaller conventional therapeutic quantities were utilized in man and were probably the result of the larger amounts used. The dissipation rate of the blood quinidine levels were consistent with those previously observed (Swisher *et al.*[39] and Yount and Rosenblum[45]) with quinidine sulfate. This would be expected since the quinidine moiety is the same in both instances and, consequently, would have the same excretion rates. The implied differences in the blood quinidine levels found after the polygalacturonate are, perhaps, due to individual patient peculiarities rather than a new characteristic of the agent.

(b) THE EFFECT ON THE ELECTROCARDIOGRAM. There is general agreement that quinidine modifies the electrocardiogram, but the exact nature of these modifications has occasionally been disputed (Cheng *et al.*[7]). The electrocardiogram, nevertheless, remains the best means of defining the therapeutic effects of quinidine and certain electrocardiogram changes are generally accepted as more or less characteristic. The study of the effects on the heart of both the high dosage levels (in dogs) and therapeutic quantities (in man) of the test compound and quinidine sulfate provided the opportunity to analyze critically the electrocardiographic changes produced.

While a more rapid onset of the electrocardiographic effects was observed in the dog on high dosage levels, this was not apparent in man on therapeutic dosage schedules. In both the dog and man there was no appreciable quinidine accumulation and the effects, with almost no exceptions, disappeared within 48 hours after the discontinuance of the drug. On equivalent quinidine dosage, there was no difference either qualitatively or quantitatively in the electrocardiographic changes produced by quinidine sulfate and quinidine polygalacturonate in man.

Both quinidine sulphate and quinidine polygalacturonate produced the same qualitative and quantitative changes in the electrocardiogram of the dog. The only noticeable variation was the time of onset of these changes. In the dog, quinidine sulfate caused the electrocardiographic changes to appear earlier than did quinidine polygalacturonate. In humans, on a therapeutic dosage schedule, no difference was discerned between the onset and general effects of these compounds.

In the dog, at the dosage level of 100 mg. of quinidine alkaloid per kg. body weight, both quinidine sulfate and polygalacturonate produced notching

and increased amplitude of P wave, with an almost universal increased width of the QRS complex, accompanied by certain peculiar and common modifications (Fig. 6). With the widening of QRS complex, there was noted a notching of the R spike near its apex and a striking reciprocity between a higher amplitude of the QRS_2 and a lower amplitude of the QRS_1 complexes. Changes in Lead III followed those of Lead II but were less marked.

The T waves in Lead I frequently

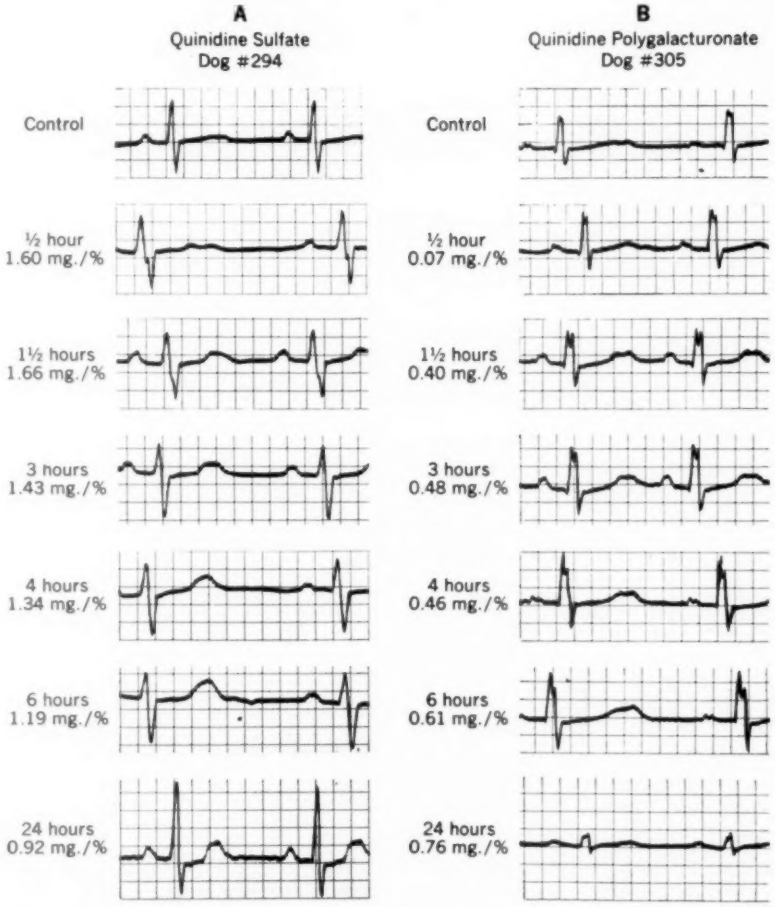


Fig. 6.—The electrocardiographic changes (Lead II) in the dog, after the administration of 100 mg. of quinidine base equivalent of quinidine sulfate and quinidine polygalacturonate, per kg. body weight.

A. Dog #294 (quinidine sulfate). Note prolongation of P wave, QRS complex and the development of U wave with unbilicated T–U wave complex.

B. Dog #305 (quinidine polygalacturonate). Similar electrocardiographic changes were observed to that in A, but these do not occur in the same magnitude until 3 to 4 hours after administration.

The first quinidine electrocardiogram effects were observed within ½ hour after the administration of quinidine sulfate and 1½ hours after the administration of quinidine polygalacturonate.

became inverted, while in Lead II (and again to a lesser degree in Lead III) the T waves would become upright where they had been flat or inverted previously. Gold[16] has noted similar changes, pointing out "the tendency for a negative T wave to become less negative" and as the dose of quinidine is increased to become a high positive T wave.

Great care in interpretation of T wave changes proved necessary because one of the most characteristic responses to quinidine was the development of a U wave which could easily be confused with the T wave (Cheng *et al.*[7]).The U wave appeared before the T wave changes and the exact delineation and separation could only accurately be accomplished by measuring the control QT interval. Thus, what often cursorily appeared to be a change in T wave was actually the production of a U wave, which in all cases, preceded an increase in T wave positivity. Later, a coalescence of both to form a tall, broadened T–U complex, umbilicated on the upper margin, occurred. Finally short-lived, slight to moderate ST depression most marked in Lead II, and present only during the period of high quinidine blood levels frequently appeared.

In man, both quinidine sulfate and quinidine polygalacturonate produced changes in all of the components of the electrocardiogram. There was a progressive depression of ST segment in the standard leads, widening of the QRS complex and the development of a more prominent U wave, particularly in the mid precordial leads. However, in contradistinction to what occurs in the dog (Leads II, III) there is a frequent depression or inversion of T wave. In dogs there was an infrequent, fleeting prolongation of PR interval. A similar situation occurs in man as a result of quinidinization when large doses have produced different degrees of AV block. Gold[16] reported an occasional widening of P wave in man and we found corresponding widening of P wave in some of the dogs' electrocardiograms. With increasing quinidine dosage levels, AV block may occur and premature contractions from variable foci may be produced. While ectopic rhythms have also been observed in occasional instances with large doses of quinidine, these were not evident in our present study. As a result of quinidine administration for atrial flutter or atrial fibrillation, the atrial movements were slowed and the atrial oscillation of the fibrillation became increasingly coarser. In atrial flutter the atrial rate may slow to the extent that atrial standstill can occur.

(c) ANTIARRHYTHMIA PROPERTIES: Quinidine polygalacturonate causes a therapeutic response similar to that of quinidine sulfate in the conversion of certain arrhythmias (Table 1) (Figs. 7 and 8). In our present series, which included 21 patients with atrial fibrillation, 16 (76%) were successfully converted to a sinus mechanism within 12 to 72 hours. The failures were all in patients with chronic fibrillation, previously found refractory to quinidine sulfate. Increasing the dosage in these patients produced no additional conversions. Of the 16 successful conversions, 7 occurred within 12 to 24 hours. Five patients required 24 to 48 hours for conversion to a sinus mechanism and 4 reverted to a normal rhythm within 72 hours. Nine of the 16 successful conversions occurred with the "rapid" method (0.4 gm. every 2 hours for 5 doses). The remaining 7 received 0.4 gm. three to four times daily. After a sinus mechanism had been established, the patients were placed on a maintenance dose of 0.2 gm. two to three times daily, and this

dosage level maintained a sinus mechanism in 10 of the group.

Of the 6 patients who relapsed into arrhythmia, 3 had discontinued their quinidine maintenance dose for at least 6 weeks. These were reconverted to sinus rhythm by resumption of quinidine polygalacturonate. The other 3 developed congestive heart failure, but after digitalization they were reconverted to a sinus mechanism by the further administration of quinidine.

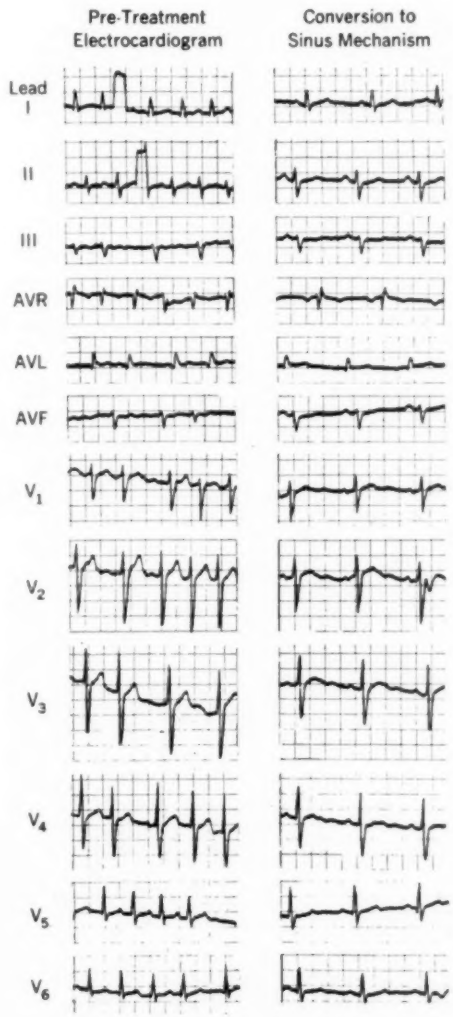


Fig. 7.—S.L., a 56-year-old white male developed an atrial fibrillation during thyroid and Dexedrine therapy for obesity. Quinidine polygalacturonate, 0.2 gm. (equivalent), t.i.d., was administered and the patient converted to a sinus mechanism approximately 48 to 72 hours after institution of therapy. The sinus mechanism was maintained, when quinidine polygalacturonate was discontinued one week later. Thyroid and Dexedrine therapy was reinstituted at one-half the previous dosage level and the sinus rhythm continued without further cardiac rhythm aberrations. (Note the change in the contour of the T waves with development of T–U complex, in the mid-precordial leads, after quinidine therapy).

TABLE 1.—THE CLINICAL PROPERTIES OF QUINIDINE POLYGALACTURONATE

Arrhythmia	#	*M*	*F*	*Age Range yrs.*	*Underlying Heart Disease**	*Duration of Arrhythmia*	*Starting Dosage†*	*Results*
Atrial Fibrillation	21	8	13	23–74	ASHD-13 HTHD-5 RHD–3	Less than 6 mos.-12 1–2 yrs.–4 2–5 yrs.–3	0.2 gm.(tid or 0.4 gm.) qid–11 0.4 gm. q. 2 hrs. for 5 doses–10	Converted–16 Failures–5 Relapsed–5 (converted on higher maintenance dose)
Atrial Flutter	2	2	—	45–58	RHD ASHD	Less than 6 mos.–1 1–2 yrs.–1	0.4 gm., qid	Converted–2
Paroxysmal Atrial Fibrillation	5	3	2	31–63	Unknown–1 HTHD–2 ASHD–2	1 yr.–2 3 yrs.–2	0.4 gm., qid	Converted–5
Paroxysmal Atrial Tachycardia	8	2	6	21–52	HTHD–2 RHD–4 Unknown–2	Less than 1 yr.–4 2 yrs.–2 more than 2 yrs.–2	0.4 gm., qid	Normal rate without recurrence–6 1 had two attacks in 2 mos. 1 required 0.4 gm., tid for maintainance
Premature Atrial Contractions	4	1	3	33–76	HTHD–2 ASHD–2	1 yr.–1 3 yrs.–2	0.4 gm., tid or qid	Premature beats disappeared–3; decreased–1
Premature Ventricular Contractions	9	4	5	14–80	ASHD–3 RHD–5 HTHD–1	1 yr.–3 2 yrs.–1 5 yrs.–4 more than 5 yrs.–1	0.4 gm., tid or qid	Premature beats disappeared–6; decreased–3
Premature Ventricular Beats of Multifocal Origin	1	1	—	55	Unknown–1	1 yr.–1	0.4 gm., qid	Premature beats decreased

* ASHD, (Atherosclerotic Heart Disease); HTHD, (Hypertensive Heart Disease); RHD, (Rheumatic Heart Disease)
† All dosages are expressed in equivalent quinidine base content to that of the indicated amount of quinidine sulfate

The clinical effects obtained with quinidine polygalacturonate in converting an atrial fibrillation are in good agreement with those reported for quinidine sulfate. Holzman and Brown[20] summarized the average rate of successful restoration of normal rhythm in a series of 1,082 unselected cases of atrial fibrillation (gathered from the literature) as 71%, with indi-

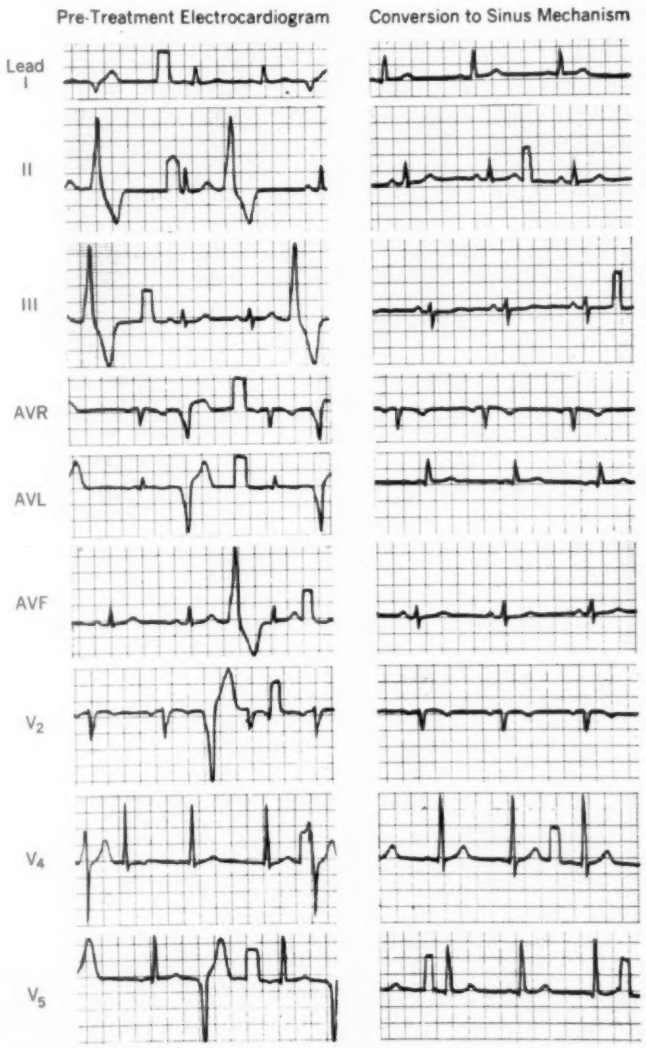


Fig. 8.—A.R., a 62-year-old white male with no organic heart disease complained of palpitations occurring for the past 2 years. The electrocardiogram revealed frequent premature ventricular contractions, often in bigeminy and trigeminy. After quinidine polygalacturonate 0.2 gm. (equivalent, q.i.d.) for 3 days the premature beats disappeared. With the reduction of the dosage to 0.2 gm. to 0.4 gm. daily, the patient maintained a regular sinus mechanism without premature beats.

vidual series variations of from 53 to 89%.

The tendency for relapse after successful therapy is well known and is often related to the severity of the clinical disease. When no maintenance therapy is prescribed, the relapse rate may be as high as 70 to 75% (Holzman and Brown[20]). However, when quinidine is given continuously (in maintenance dose), the relapse rate is markedly diminished. Kohn and Levine[24] report that a 49% relapse rate was observed when 0.2 gm. of quinidine sulfate is administered two to three times daily and Sokolow[37] attributed his rather low recurrence rate of 20% to a maintenance regimen of 0.4 gm., three or four times daily.

All of the 5 patients with paroxysmal atrial fibrillation studied were successfully converted to sinus mechanism within 12 to 24 hours on a dosage regimen of 0.4 gm. of quinidine polygalacturonate, four times daily. The normal rhythm was maintained with a dosage schedule of 0.2 gm., two or three times daily.

Eight patients with paroxysmal atrial tachycardia were treated with quinidine polygalacturonate, 0.4 gm., q.i.d., and in 6 of these patients the tachycardia disappeared and there was no recurrence of the arrhythmia while these patients remained on a maintenance dosage of quinidine polygalacturonate, 0.2 gm., b.i.d. The two unsuccessful attempts continued to show atrial rate aberrations and, on increased dosage (0.4 gm., t.i.d.), one patient was free of attacks for a 2-month period while the other had two occurrences during this period.

A dosage regimen of 0.4 gm., three times daily converted 2 patients with atrial flutter and there was no reappearance of the flutter during maintenance therapy.

Of the 9 patients with premature ventricular contractions, 0.4 gm., four times daily, caused a disappearance of premature ventricular beats in 4 patients and reduced the incidence of premature beats in the remaining 5. Three of the latter group of 5, showed a disappearance of the premature beats when the dosage was increased to 0.4 gm. every 2 hours for three doses. There was no appreciable change in the remaining 2 on increased dosage. The 4 patients with premature atrial contractions and the one patient with premature beats of a multifocal origin all responded to therapy with a disappearance of the arrhythmia in 3 patients and a lessening of the premature beats in the remaining 2 patients (Figs. 9 and 10).

(d) GASTROINTESTINAL EFFECTS. There were no instances of gastrointestinal distress reported by the patients receiving quinidine polygalacturonate, either on the rapid regimen whereby 30 grains are administered within 10 hours or on chronic administration. In 2 patients, with paroxysmal atrial fibrillation, who had previously encountered nausea and vomiting with quinidine sulfate, the new agent caused no such effect when administered in equivalent and even higher dosage. Similarly, there was no local irritative effects evidenced by those patients receiving chronic maintenance medication during the 6 months course of this study. Five patients received nine grains (0.6 gm.) three times daily for periods up to 5 days without evidence of local gastrointestinal distress.

It would appear that the problem of local irritation is adequately controlled by the new quinidine polygalacturonate. However, it should be constantly borne in mind that gastrointestinal symptoms may also arise from a central origin. Since the centrally mediated excitation of the gastrointestinal tract is a function of absorbed

Fig. 9.—M.D., a 72-year-old white woman with arteriosclerotic heart disease, revealed a nodal tachycardia with frequent premature supraventricular beats in the admission electrocardiogram. The patient was given a single dose of 0.6 gm. (equivalent) of quinidine polygalacturonate and serial electrocardiograms revealed such typical quinidine effects as PR prolongation; depression of ST segment and a widened T (or T–U) complex in the mid-precordial leads. There was a gradual and progressive disappearance of premature beats with the return of an essential sinus mechanism at 4 hours. The first quinidine effects were observed to begin within 1 to 1½ hours after drug administration with a slight depression of the ST segment and moderate reduction in premature beats. All ECG changes became fully developed at 4 hours with virtual absence of premature beats. It is of interest to note that in this patient, at the dosage level administered, there was no appreciable prolongation of QRS complex. A gradual return to the pre-treatment status was observed as the quinidine blood levels decreased, beginning at 12 hours, and was virtually complete at 24 hours.

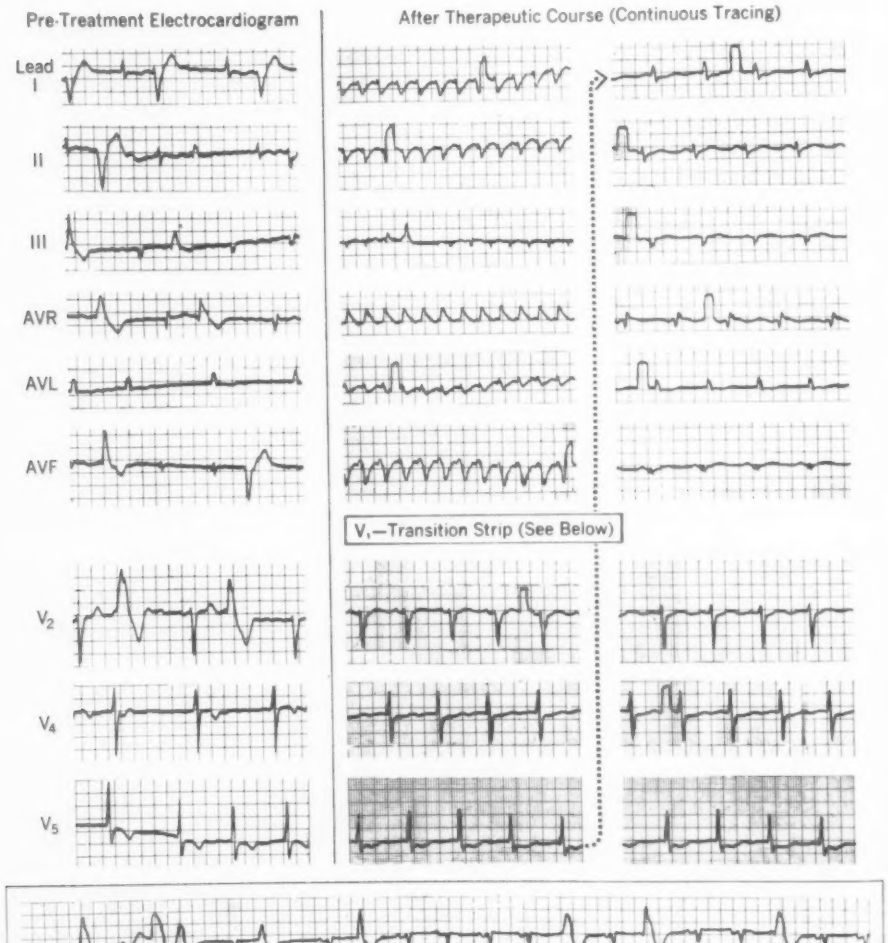


Fig. 10.—J.P., a 55-year-old white male with arteriosclerotic heart disease and atrial fibrillation with multifocal premature ventricular contractions, had been taking digitoxin (0.2 mg.) daily for several months. At the time of examination, the QRS complex measured 0.10 seconds in the conventional leads. Quinidine polygalacturonate, 0.4 gm., every 2 hours for 5 doses, was prescribed in an attempt to eliminate the multifocal premature beats which were considered to be a serious hazard. The electrocardiogram taken at the conclusion of the therapeutic course (8 hours after first dose) revealed the development of a ventricular tachycardia with a QRS widened to 0.16 second. As the continuous strip was being taken, the patient spontaneously converted to a sinus mechanism with frequent unifocal premature beats (as seen in Lead V_1 transition strip) and then immediately (and subsequently) maintained a sinus mechanism without any premature beats. The QRS complex after this conversion again measured 0.10 second.

quinidine and not of a local action, the occurrence of gastrointestinal symptoms will arise when sufficiently large amounts are administered.

Summary and Conclusions. 1. Quinidine polygalacturonate was studied in both animals and humans with regard to its absorption, electrocardiographic effects and antiarrhythmic properties.

2. While a sustained rate of absorption of the polygalacturonate was observed in animals on high dosage, this was not noted when therapeutic quantities were administered to man. The pattern of absorption of quinidine polygalacturonate appeared to be similar to that of quinidine sulfate. Both quinidine sulfate and quinidine polygalacturonate produced identical changes in the electrocardiograms of both dogs and man. While the electrocardiographic effects were observed to appear earlier after a high dosage of quinidine sulfate in dogs, this was not observed in man when the lower therapeutic quantities of the compounds were utilized.

3. Quinidine polygalacturonate is capable of causing the full pharmacodynamic therapeutic action of quinidine in correcting disturbances of the cardiac rhythm. This compound was well tolerated without incidence of any untoward side reactions.

4. By preserving the cardiodynamic properties of quinidine with the reduction of the incidence of local gastrointestinal distress, it is hoped that this valuable drug may be salvaged for use in the many cardiac patients who have been denied its therapeutic benefits because of the occurrence of local gastrointestinal distress.

REFERENCES

1. **Acierno, L. J.,** and **Gubner, R.:** Am. Heart J., **41,** 733, 1951.
2. **Archer, H. C., Weitzman, D.,** and **Kay, H. L.:** Brit. Heart J., **17,** 534, 1955.
3. **Berger, H. H.:** Am. Heart J., **41,** 624, 1951.
4. **Blinder, H., Burstein, J., Horowitz, W., Gersh, E.,** and **Smelin, R.:** A.M.A. Arch. Int. Med., **86,** 917, 1950.
5. **Brown, M. G., Holzman, D.,** and **Creelman, E. W.:** Am. J. Med. Sci., **255,** 129, 1953.
6. **Calesnick, B., Smith, N. H.,** and **Beutner, R.:** J. Pharmacol. & Exper. Therap., **102.** 138, 1951.
7. **Cheng, T. O., Sutton, G. C., Swisher, W. P.,** and **Sutton, D. C.:** Am. Heart J., **51,** 417, 1956.
8. **Cohn, A. E.,** and **Levy, R. L.:** Proc. Soc. Exper. Biol. & Med., **18,** 283, 1920–21.
9. **Crimm, P. D., Westra, J. J.,** and **Thompson, R. E.:** Am. Rev. Tuberc., **47,** 493, 1943.
10. **Dawes, G. S.:** Pharmacol. Rev., **4,** 43, 1952.
11. **Ditlefsen, E. M.:** Acta med. Scandinav., **149,** 49, 1954.
12. Idem: Ibid., **146,** 81, 1953.
13. **Ditlefson, E. M.,** and **Knutsen, B.:** Ibid., **156,** 8, 1956.
14. **Ernstene, A. C.,** and **Lowis, S.:** J. Pharmacol. & Exper. Therap., **48,** 305, 1933.
15. Idem: Ibid., **48,** 359, 1933.
16. **Gold, H.:** Quinidine in Disorders of the Heart. New York: Paul B. Hoeber, Inc., pp. 13, 16, 1950.
17. **Halpern, A., Shaftel, N.,** and **Montebovi, A. J.:** To be published.
18. **Halpern, A., Shaftel, N.,** and **Schwartz, G.:** To be published.
19. **Hiatt, E. P.,** and **Quinn, G. P.:** J. Pharmacol. & Exper. Therap., **83,** 101, 1945.
20. **Holzman, D.,** and **Brown, M. G.:** Am. J. Med. Sci., **222,** 644, 1951.
21. **Kalmansohn, R. W.,** and **Sampson, J. J.:** Circulation, **1,** 569, 1950.
22. **Kertesz, Z. I.:** The Pectic Substances. New York: Interscience Publishers, Inc., p. 393, 1951.
23. **Kobren, A., Fellers, C. R.,** and **Esselson, W. B., Jr.:** Proc. Soc. Exper. Biol. & Med., **41,** 117, 1939.

24. **Kohn, C. M.,** and **Levine, S. A.:** Ann. Int. Med., **8,** 923, 1935.
25. **Kwit, N. T.,** and **Gold, H.:** J. Pharmacol. & Exper. Therap., **50,** 180, 1934.
26. **Lewis, T., Drury, A. N., Iliescu, C. C.,** and **Wedd, A. M.:** Heart, **9,** 55, 1921.
27. **Linenthal, A. J., Ulick, S.,** and **Patterson, L. A.:** J. Clin. Invest., **26,** 1188, 1947.
28. **Malyoth, G.:** Klin. Wchnschr., **13,** 51, 1934.
29. **Manville, I. A.:** Arch. Pediat., **55,** 76, 1938.
30. **Manville, I. A., Reithel, F. J., Yamada, P. M., Spencer, T. W.,** and **Richardson, J. R.:** J. Indust. Hyg. & Toxicol., **22,** 36, 1940.
31. **Miller, L. C.,** and **Tainter, M. L.:** Proc. Soc. Exper. Biol. & Med., **57,** 261, 1944.
32. **Russek, H. I.,** and **Zohman, B. L.:** J. Am. Med. Assn., **147,** 1070, 1951.
33. **Sampson, J. J., Foreman, H.,** and **Solomon, B. C.:** Circulation, **5,** 534, 1952.
34. **Shaftel, N.,** and **Halpern, A.:** Angiology, **9,** 34, 1958.
35. **Sokolow, M.:** Am. Heart J., **52,** 771, 1951.
36. Idem: Ann. Int. Med., **45,** 582, 1956.
37. **Sokolow, M.,** and **Ball, R. E.:** Circulation, **14,** 568, 1956.
38. **Sollmann, T.:** A Manual of Pharmacology, 8th ed. Philadelphia: W. B. Saunders Co., p. 706, 1957.
39. **Swisher, W. P., Wedell, H. G., Cheng, J. T. O., Sutton, G. C.,** and **Sutton, D. C.:** Am. Heart J., **47,** 449, 1954.
40. **Tompkins, C. A.,** and **Howard, P. J.:** Am. Med. Assn., **114,** 2355, 1940.
41. **Wegria, R.,** and **Boyle, M. N.:** Am. J. Med., **4,** 373, 1948.
42. **Weisman, S. A.:** Am. Heart J., **20,** 21, 1940.
43. **Weiss, S.,** and **Hatcher, R. A.:** J. Pharmacol. & Exper. Therap., **30,** 335, 1927.
44. **Winters, M., Peters, G. A., Crook, G. W.:** Am. J. Dig. Dis., **6,** 12, 1939.
45. **Yount, E. H.,** and **Rosenblum, M.:** South. Med. J., **43,** 324, 1950.

SUMMARIO IN INTERLINGUA

Le Studio Clinic De Polygalacturonato De Quinidina

1. Polygalacturonato de quinidina esseva studiate, tanto in animales como etiam in humanos, con respecto a su absorption, su effectos electrocardiographic, e su virtutes anti-arrhythmic.

2. Durante que le absorption del polygalacturonato se monstrava perdurative e uniforme in canes recipiente lo in alte dosage, isto non esseva notate quando quantitates therapeutic esseva administrate a humanos. Le procedimento del absorption de polygalacturonato de quinidina pareva esser simile a illo de sulfato de quinidina. Ambe drogas produceva alterationes identic in le electrocardiogrammas, tanto in canes como etiam in humanos. In canes recipiente alte doses de sulfato de quinidina, le effectos electrocardiographic esseva plus prompte in comparation con le altere droga, sed iste differentia non esseva notate in humanos recipiente le plus basse doses therapeutic del duo compositos.

3. Polygalacturonato de quinidina es capace de producer le complete effecto therapeutic pharmacodynamic de quinidina in corriger le disturbationes del rhythmo cardiac. Iste composito esseva tolerate sin incidentia de adverse reactiones lateral.

4. Viste que polygalacturonato de quinidina possede le proprietates cardiodynamic de quinidina sed distingue se per un reduction del indicentia de local disturbationes gastrointestinal, il es a sperar que quinidina in le forma del galacturonato va esser salvate pro le uso in omne le numerose casos de patientes cardiac qui ha debite passar se del beneficios therapeutic de quinidina a causa del occurrentia de local disturbationes gastrointestinal.

SUMMARIO IN INTERLINGUA

(See page 208 for original article)

Phagocytose De Cryoglobulina Observationes In Cellulas A Inclusion Crystallin

1. Crystallos intraleucocytic esseva observate in preparatos a cellula "L.E." ab patientes con cryoglobulinemia.

2. Iste crystallos pote esser vidite solmente quando le leucocytos e le sero es incubate a 37 C. Le phenomeno ha essite interpretate como le resultato de phagocytose de cryoglobulina non-crystallin, sequite per crystallisation intracellular.

3. Le natura proteinic del crystallos es suggerite per le resultatos de studios immunologic.

4. Le phenomeno pote esser utilisate como proba sensibile e apparentemente specific in le demonstration de micre quantitates de cryoglobulina.

5. Le signification pathologic e clinic de leve grados de asymptomatic cryoglobulinemia non es clarmente establite, sed il pare que su occurrentia es relationate a disordines del systema reticuloendothelial. Il es a sperar que le disponibilitate de un simple test, como illo hic describite, va stimular studios additional visante a clarificar le signification clinic de cryoglobulina.

ACUTE TOXICITY AND TREATMENT OF INTOXICATIONS DUE TO CROTALUS ADAMANTEUS (RATTLESNAKE VENOM)

By William B. Deichmann, Ph.D.
PROFESSOR OF PHARMACOLOGY

J. L. Radomski, Ph.D.
ASSOCIATE PROFESSOR OF PHARMACOLOGY

J. J. Farrell, M.D.
PROFESSOR OF SURGERY

William E. MacDonald, M.A.
INSTRUCTOR IN PHARMACOLOGY

AND

M. L. Keplinger, Ph.D.
RESEARCH ASSISTANT PROFESSOR OF PHARMACOLOGY

(From the Departments of Pharmacology and Surgery, University of Miami School of Medicine, Coral Gables, Florida)

Several reports have appeared in the literature of the apparently successful therapy of snake bite with the glucocorticoid hormones (Hoback and Stern[2], and Wood, Hoback and Green[3]). These, and especially a local case of rattlesnake bite which was successfully treated with hydrocortisone (Dees[1]) suggested that the effectiveness of a glucocorticoid be evaluated in a well-controlled animal experiment in which other therapeutic factors could be eliminated.

The acute toxicity of *Crotalus adamanteus* was determined in a number of species to provide a background of information for these experiments.

Methods and Materials. All venoms were purchased from William Haast of the Miami Serpentarium, Miami, Florida. At this institution snakes are milked at weekly intervals. A venom is placed in a Petri dish in a $CaCl_2$ desiccator, suction is then applied for approximately 12 hours. This process removes 75 to 80% of moisture leaving the venom in crystalline form. The venom is then stored at 0° C. until used. It apparently keeps indefinitely at this temperature. *Crotalus adamanteus* was prepared for intramuscular injection as a solution in normal saline (0.05 to 2.0%, wt. per vol.) and stored in a refrigerator until used.

Experimental. The following species were employed for the determination of the *Approximate Lethal (IM) Dose* of *Crotalus adamanteus*: adult mongrel dogs, rhesus monkeys, albino rabbits, Sprague-Dawley rats, CWF white mice, guinea pigs and pigeons, 4-week old Rhode Island Red chicks and 5-week old pigs of mixed breed. The method of Wm. B. Deichmann and T. J. LeBlanc was employed for the determination of the *Approximate Lethal Dose*. (J. Indust. Hyg. and Toxicol., **25**, 415, 1943; **30**, 373, 1948). All animals were kept supplied with food and water at all times. The surviving animals were kept under observation for 14 to 20 days, then discarded.

Dogs were used for the cortisone studies. They were housed in pens of approximately 8′ × 8′, they were not restrained at any time and did not receive supportive therapy. Hydrocortisone (Hydro-Cortef) was injected intravenously. An initial dose of 100 mg. per dog was administered either immediately after the intramuscular injection of two *Approximate Lethal Doses* of *Crotalus adamanteus* (1.28 mg. per kg.) or, 2 and 4 hours respectively, after injection of the venom. Each dog received subsequently 50 mg. of Hydro-Cortef once a day for several days.

Results. ACUTE TOXICITY. Almost immediately after an intramuscular injection into the thigh muscles, a dog appeared to suffer marked local pain. This lasted for 30 minutes to 2 hours. Generalized mild tremors followed, together with a mild degree of muscular weakness, salivation and an increased rate of respiration. Dogs that succumbed became more and more lethargic. They died in coma without convulsions in from 18 to 24 hours. There was one exception, a dog that received 0.64 mg. per kg. and which survived for 3 days. Dogs that received sublethal doses remained in a generalized depressive state for 3 to 4 days, then began to recover.

Locally, the injection of the venom (0.08 to 1.4 mg. per kg. in 2 to 7 ml. of saline) induced an immediate swelling. The severity of the edema increased for about 3 hours until the thigh (site of injection), lower leg and even toes had assumed nearly twice the normal size. After 3 to 4 days the skin ruptured at the site of injection or on the inner side of the leg and somewhat lower. Openings in the skin (4 to 15 cm. in length) exposed the underlying "digesting" skeletal muscles. Serosanguineous fluid and pus oozed from such wounds as long as there was evidence of edema. This lasted approximately 2 weeks. Healing then began and was complete in 4 to 6 weeks.

In addition to the local and systemic effects presented, the dogs demonstrated a more or less severe bloody diarrhea. This became apparent on the day following the injection of the venom and subsided with the disappearance of the edema. All surviving dogs lost some body weight during the first 2 weeks, even though their appetite on the whole remained good. They moved about freely with the exception of the first few days.

All other species presented essentially the same local and systemic effects (Table 1).

EFFECT OF CORTISONE. Table 2 presents the data on the treatment of *Crotalus adamanteus* intoxication with Hydro-Cortef. All 4 dogs, that received the first dose of Hydro-Cortef immediately after the injection of the venom, survived. These animals received doses of cortisone ranging in total from 450

YIELD OF VENOM EJECTED BY 12 SPECIMENS OF *CROTALUS ADAMANTEUS* NOT PREVIOUSLY HANDLED. (COURTESY OF WM. HAAST)

Length of Snake		*Approximate Weight of Venom Voided in One Bite*	
	Weight	*Crystalline*	*Natural*
cm.	*kg.*	*mg.*	*gm.*
58.4	0.113	20	0.08
106.7	0.879	100	0.4
115.6	1.162	130	0.5
120.7	1.191	60	0.2
119.4	1.219	120	0.5
135.9	1.559	160	0.6
146.1	1.673	110	0.4
132.1	1.701	280	1.1
135.9	1.786	240	1.0
146.1	1.956	300	1.2
123.2	2.155	240	1.0
149.9	2.949	160	0.6
		Mean	0.654

to 650 mg. per dog. Of the second group, 65% (13 of 20 dogs) survived. These animals received the first dose of cortisone 2 hours after injection of the venom. Total doses of cortisone ranged in this group from 200 to 550 mg. per dog. The third group received the first dose of Hydro-Cortef 4 hours after the venom. In this group, the percentage of survivals was even higher (9 of 12 dogs, or 75%). These animals received a total of 200 to 450 mg. of cortisone. No reasonable explanation can be offered for the higher percentage of survivals in this latter group. The ratio might have been less favorable had the same number of dogs been used as in the previous group, namely 20. The differences in these two experiments cannot be explained on a basis of sex, body weight, breed or nutritional condition of a dog. An additional group of dogs served as control. Each of the 12 animals in this group (as well as each dog in the experimental groups) was given an intramuscular injection equal to 1.28 mg. per kg. of the crystalline venom. It was assumed that this dose, which is equal to twice the *Approximate Lethal Dose*, would represent an LD_{100}, but it turned out to be an LD_{83}.

TABLE 1.—THE APPROXIMATE LETHAL (INTRAMUSCULAR) DOSE OF *CROTALUS ADAMANTEUS*

Species	*Number of Animals Treated*	*Approximate Lethal Dose*			*Lethal Doses in "One" Average Snake Bite*° *per Species*	*Period of Survival hrs.*
		Crystalline Venom mg./kg.	*Natural Venom*			
			mg./kg.	*mg./animal*		
Dog (10 kg.)	8	0.64	2.8	28.0	12	18 to 72
Goat (5 kg.)	7	0.64	2.8	14.0	23	4 to 36
Rhesus Monkey (2.5 kg.)	7	0.64	2.8	7.0	46	4 to 36
Albino Rabbit (3 kg.)	18	0.94	4.1	12.0	27	10 to 24
Pigeon (340 gm.)	9	1.4	6.2	2.0	162	2 to 18
Chick (200 gm.)	24	1.4	6.2	1.5	216	5 to 18
Guinea Pig (400 gm.)	12	3.2	14.0	6.0	54	3 to 40
Pig (7 kg.)	6	3.2	14.0	98.0	4	3 to 18
Albino Mouse (20 gm.)	10	10.7	47.0	1.0	325	48 to 72
Albino Rat (200 gm.)	71	25.0	110.0	22.0	15	30 to 36

°Based on the assumption that two *Approximate Lethal Doses* represent an LD_{100}.

Conclusions. 1. The intramuscular injection of *Crotalus adamanteus* (rattlesnake venom) is followed by the immediate production of local and systemic effects. Local effects at or near the site of injection include: marked edema (and apparently marked pain), followed by rupture of the skin, digestion of the skeletal muscles, and necrosis. Systemic effects are confined to general lethargy, salivation, bloody diarrhea and death in coma.

2. The acute toxicity (intramuscular) of the crystalline venom (20 to 25% of original weight) varies considerably for different species. The *Approximate Lethal Doses*, in mg. per kg. are as follows: dog, goat and rhesus monkey, 0.64 (2.8); rabbit 0.94 (4.1); pigeon and chick 1.4 (6.2); pig and guinea pig, 3.2 (14.0); mouse, 10.7 (47.0); and rat 25.0 (110.0). (Values in parenthe-

ses present lethal doses of original venom).

3. An average bite of a rattlesnake releases approximately 650 mg. of venom. This quantity is sufficient to kill approximately 4 young pigs, or 12 dogs, or 15 rats, or 23 young goats, or 27 rabbits, or 46 rhesus monkeys, or 54 guinea pigs, or 162 pigeons or 216 chicks, or 325 mice.

4. Hydrocortisone (Hydro-Cortef) injected intravenously into dogs 2 and 4 hours respectively, after an intramuscular injection of two *Approximate Lethal Doses*, (1.28 mg. per kg.) of crystalline *Crotalus adamanteus* raised the number of surviving dogs from 17% (control) to 65 and 75%, respectively. Without the benefit of cortisone, dogs died in approximately 18 hours. Those that succumbed with cortisone survived for about 3 days. On the basis of these data, a dog given *two Approximate Lethal Doses* of venom and treated subsequently with Hydro-Cortef has a slightly better than even chance to survive.

The administration of cortisone did not influence visibly the local proteolytic or septic effects or healing. The beneficial action of cortisone is not understood at present.

TABLE 2.—EFFECTS OF HYDRO-CORTEF IN THE TREATMENT OF *CROTALUS ADAMANTEUS* INTOXICATION IN THE DOG

(Each dog was given an intramuscular dose of 1.28 mg./kg. of crystalline venom equal to 5.5 mg./kg. of natural venom)

Number of Dogs Treated	*Surviving Dogs to Total No. of Dogs*		*Mean Period of Survival*
	Ratio	*Percentage*	
Solu-Cortef Given Immediately After Injection of Venom			
4	4/4	100	
Solu-Cortef Given 2 Hours After Injection of Venom			
20	13/20	65	3 days (18 hrs. to 5 days)
Solu-Cortef Given 4 Hours After Injection of Venom			
12	9/12	75	3 days (2 to 4 days)
Control: No Solu-Cortef			
12	2/12	17	18 hrs. (4 hrs. to 3 days)

REFERENCES

1. Dees, J.: Personal Communication, Department of Surgery, University of Miami School of Medicine.
2. Hoback, W. W., and Stern, T. W.: J. Am. Med. Assn., **152**, 236, 1953.
3. Wood, T. J., Hoback, W. W., and Green, T. W.: Virginia Med. Month., **82**, 130, 1955.

(Interlingua on page 249)

PHAGOCYTOSIS OF CRYOGLOBULIN*
OBSERVATIONS ON CRYSTAL-INCLUSION CELLS

By Paul Heller, M.D.

Vincent Yakulis, B.S.

Michael L. Glick, M.D.

and

Sheldon E. Krasnow, M.D.

(From the Departments of Medicine, Veterans Administration Westside Hospital, Chicago, Illinois and the University of Illinois College of Medicine, Chicago, Illinois)

The physico-chemical characteristics of cryoglobulins and the clinical significance of their presence in high concentration in the serum of patients have been thoroughly explored in many studies (Barr, Reader and Wheeler[3], Hardy and Putnam[14], Lerner and Watson[24], Mackay *et al.*[26], Mandema, Vander Schaaf and Huisman[27] Volpe *et al.*[50], and Wertheimer and Stein[53]). As cryoglobulins precipitate and frequently crystallize (Mackay *et al.*[26], Olhagen[34], and Shapiro and Wertheimer[44]) spontaneously on cooling, their presence is easily demonstrated when the concentration is high; but smaller amounts are not as readily detected. Although it has not been clearly determined if any clinical significance can be attributed to the presence of small amounts of cryoglobulin in the serum (Barr, Reader and Wheeler[3], James and Drake[17], Lerner, Barnum and Watson[25]), most authors agree that cryoglobulins are definitely abnormal proteins (Morrison, Edsall and Miller[29], and Putnam and Miyake[39]). Unfortunately, cryoglobulin, when present in only small concentration, may easily escape detection by the traditional method (Lerner, Barnum and Watson[25]) of cooling the serum. During the aspiration from the vein into a cold syringe, it may precipitate and be removed unnoticed with the packed cells or the clot. It also may be phagocytized by the leukocytes (Hutchinson and Howell[16], Volpe *et al.*[50], and Volpe and Ogryzlo[51]). The latter phenomenon is the subject of this study.

Crystals, apparently within the leukocytes, were accidently discovered in the L.E. cell preparation from a patient with "essential cryoglobulinemia" (Figs. 1 and 2). In the same smear, bluish or colorless intraleukocytic inclusion bodies were also observed. These had been previously described by Volpe and Ogryzlo[50,51] and by Hutchinson and Howell[16]. These authors have suggested that this inclusion body represents phagocytized cryoglobulin. As cryoglobulin may precipitate from the serum in the crystalline state, it appeared likely that also the observed crystals represent phagocytized cryoglobulin. A study of the mechanism of this phenomenon was undertaken to evaluate its suitability for a clinical test for the demonstration of small quantities of cryoglobulin.

Method. 1. The L.E. test was performed in the traditional manner (Zimmer and

*Aided by a grant from the Hematology Research Foundation, Chicago, Illinois.

Hargraves[56]). Minor modifications, to be described later, were necessitated by the conditions of this study. Clotted blood samples from more than 200 patients and 20 normals were examined in this way. In some of the patients, the presence of cryoglobulinemia was clinically suspected. If crystals were demonstrated, the patient's serum was also incubated with the buffy layer of normal citrated blood. This modification was chosen because it facilitated the preparation of aliquots. As the occurrence of these crystals was believed to be related to the presence of cryoglobulin, the influence of temperature on the formation of the intracellular crystals was investigated. Each sample of the leukocyte-serum suspension was divided into 4 aliquots (A_1 A_2; B_1 B_2), which were exposed to different temperatures in the following manner: Two aliquots were maintained at the same temperature for 2 hours, A_1 at 5° C. and B_1 at 37° C., and then smeared. The temperature to which the 2 other aliquots were exposed was changed after the first hour: For A_2 from 5° C. to 37° and for B_2 from 37° C. to 5° C. Smears were then prepared following this second period. Initially, incubation was carried out for 1 hour and 2 hours, and refrigeration for an equal time, but when it became apparent that no enhancement of the formation of intracellular crystals occurred in the second hour, the incubation and refrigeration period were each limited to one hour.

2. The test for the demonstration of cryoglobulin was performed in the traditional manner (Lerner, Barnum and Watson[25]). The serum samples were left in the refrigerator for up to 72 hours. The "cryocrit" (Mackay *et al.*[26]) was then determined in the Wintrobe hematocrit tube following centrifugation in the refrigerated centrifuge. The test was considered to be negative when precipitation was absent after a 72-hour exposure to 5° C. Negative sera were refrigerated for additional 96 hours; none became positive.

3. The intracellular and extracellular crystals were examined in the polarizing microscope.

4. Paper electrophoresis of the serum of each patient with cryoglobulinemia was carried out at room temperature in veronal buffer (pH 8.6, ionic strength 0.075). The following samples were used: (a) serum, (b) the redissolved cold-precipitate in saline or 0.1 N HCl, (c) the supernatant serum after removal of the cold-precipitate.

5. For the immunologic identification of the crystals as protein crystals, the agar-gel double diffusion technique of Ouchterlony was chosen[35,36], which has been widely used for the immunological characterization of pathological proteins by several investigators (Korngold[18], Korngold and Lipari[19], Korngold and Van Leeuwen[20], Rice[41], Slater, Ward and Kunkel[47], and Westendorp and Mandema[54]). This technique permits the simultaneous demonstration of precipitation reactions of an antibody with multiple antigens (or *vice versa*), and implicitly determines the immunologic similarity or lack of similarity of antigenic substances. The agar-gel plates were prepared in the following manner: 1% Noble Special Agar (Difco) in normal saline with Merthiolate and Amidoschwarz 10B added (final concentration of each 1:100 000) was poured into Petri dishes. After solidification one reservoir was cut out in the center of the agar-gel to hold the antiserum and 4 reservoirs for the antigen solutions were prepared in a distance of 1 cm. from the center well in a symmetrical pattern. Following the inoculation of the reservoirs with the appropriate solutions, the plates were incubated in a humidified atmosphere of 37° for 3 to 7 days. In case of an immune reaction, precipitation lines in the gel area between the center reservoir and the peripheral ones usually appear within 48 hours and become more distinct during the subsequent 3 to 4 days.

6. Ultracentrifugal analysis was carried out on the serum from a patient with essential macroglobulinemia (Waldenstrom[52]). The Spinco Analytical Ultracentrifuge was used. The serum was diluted 1:4 in 0.1 M. Veronal Buffer, pH 8.6. The bar angle was 40° and the picture was taken 32 minutes after reaching full speed of 59.780 rpm.*

Results. Crystals in varying number and of varying shape with rhombic, prismatic, and hexagonal forms predominant, were seen in 14 patients by the described technique (Figs. 1, 2, 3, and 4). The concentration varied from one crystal inclusion cell every third high power field to several such cells per high power field. The serum of all patients contained cryoglobulin of vary-

*We are indebted to Dr. Virgil Koenig, Department of Biochemistry, Northwestern University Medical School, who kindly performed this examination.

TABLE 1

Number	*Age, Sex, Race*	*Diagnosis*	*Clinical Data*	*Cryocrit (Wintrobe Tube)*	*Other Laboratory Tests*	*Remarks*
1	57 M N	Essential Cryoglobulinemia	Raynaud's phenomenon for 9 years. Recurrent ulceration of both legs for 4 years. Relentless downhill course characterized by gangrene of lower extremities and fingers necessitating amputation of both legs and of several fingers within a period of 2 years. Several months prior to death, hematuria led to detection of carcinoma of bladder. Death in uremia.	30 mm.	CBC: normal Alb.: 4.1 Glob.: 3.6 Thymol Turbidity 13.4 Maclagan Units. Terminally anemia and uremia	Histology of amputated extremities: Fibrosis and hyalinization of intima of large vessels. Perivascular inflammation. Hyalinized thrombi in perivascular capillaries. No complete thrombotic occlusion.
2	57 M Cauc.	Macroglobulinemia	Chronic fatigue. Small parotid tumor for 1 year. Preoperative work-up revealed anemia, spontaneous gelling of serum. Operation was deferred. Patient's clinical state has not worsened during the year since diagnosis.	Trace	Hb: 9.25 RBC: 2.62 mill. WBC: 3,950 with slight left shift. Bone Marrow: Slightly hypercellular with moderate increase of lymphocytes and eosinophils. Glob.: 4.9 gm.% Prothrombin Time: 17 sec. (control 14 sec.) No other coagulation defects.	Results of ultracentrifugal analysis described in text.
3	46 M Cauc.	Subacute Bacterial Endocarditis	Occasional vague arthralgia for 14 years. Progressively severe dyspnea for 1 month. Phys. Ex.: HR: 108/min. No Fever. B.P.: 120/50. Clubbing. Murmurs of aortic insufficiency and stenosis. Slightly enlarged spleen. No splinter hemorrhages.	Trace	WBC: 5,850 with left shift. Hb.: 9 gm. Hematocrit 31% Serum Albumin: 2.3 Globulin: 5.1 Negative blood cultures.	Necropsy: Severe destruction of aortic valves. Cultures have remained sterile.

Progressive left and right heart failure. Blood cultures negative. Treated with 12 mill. units of penicillin, 2 gm. streptomycin, 2

			insufficiency and stenosis. Slightly enlarged spleen. No splinter hemorrhages.		Negative blood cultures.	
			Progressive left and right heart failure. Blood cultures negative. Treated with 12 mill. units of penicillin, 2 gm. streptomycin, 2 gm. Benemid daily. No improvement. Convulsive seizure and death 9 days after admission.			
4	47 M Cauc.	Subacute Bacterial Endocarditis	History of rheumatic fever at age 17. Exertional dyspnea of 3 weeks' duration. Murmurs of aortic stenosis and insufficiency. B.P. 150/70. Mild left and right heart failure. Purpuric lesions on anterior surface of both legs. Gradual improvement on penicillin and streptomycin.	Trace	Hb: 6 gm. WBC: 12,450 with left shift. Alb.: 3.3 Glob.: 3.5 Thymol Turbidity: 17 Maclagan Units. Blood cultures remained negative.	Cryoglobulin disappeared with clinical improvement.
5	75 F Cauc.	Multiple Myeloma	Anorexia and malaise for 3-4 months. Pain in right chest for several days. Progressive cachexia. Death, 4 months after diagnosis.	30 mm.	Hb.: 11 gm. Bone Marrow: Hyperplastic, 70% plasma-cells, mostly in sheets. Alb.: 2.9 Glob.: 6.4 Electrophoresis: Homogeneous gamma peak. Typical bone lesions of skull and ribs.	Fig. 5 demonstrates electrophoretic pattern with the gamma-peak which consists mainly of cryoglobulin. No Bence-Jones protein in urine.
6	57 M Cauc.	Cryptogenic fever. Periarteritis nodosa? Pyelonephritis?	Prostatectomy 2 years prior to admission. Recurrent attacks of chills and fever. Slight weight loss. Physical examination has remained negative.	Trace	Persistent eosinophilia of 600–1,000 cells per c.mm. Glob.: 2.8 Urinary sediment: no cells or casts. IVP: Normal Urine cultures: negative.	

TABLE 1 *(Continued)*

Number	*Age, Sex, Race*	*Diagnosis*	*Clinical Data*	*Cryocrit (Wintrobe Tube)*	*Other Laboratory Tests*	*Remarks*
7	47 M Cauc.	Rheumatoid Arthritis	Arthritis for 2 years. Raynaud's phenomenon of fingers for 1 year, especially on cold exposure.	Trace	Glob.: 2.1 No abnormal findings. L.E. Test: negative.	
8	75 M Cauc.	Subacute Granulocytic Leukemia	Pallor of several weeks' duration. Rapid worsening. Hemorrhagic manifestations. Death due to pneumonia.	Trace	Hb.: 10 gm. WBC: 6,700 15% blast cells 1% myelocytes 70% granulocytes 14% lymphocytes Alb.: 3.6 Glob.: 2.1 Electrophoretic Pattern: no homogeneous peak.	
9	45 M Cauc.	Laennec's Cirrhosis Acute Hemorrhagic Pancreatitis	Severe alcoholic. Repeated attacks of abdominal pain. Pleural effusion, assumed to be secondary to abdominal suppuration (pancreatic abscess). Laparatomy revealed acute pancreatitis with extensive fat necrosis. Patient died 6 weeks later.	Trace	High amylase in serum, urine, and pleural fluid. Calcium: 7.8 mg.% Glob.: 3.2 gm.% Persistent leukocytosis. Staph. aureus in peritoneal fluid.	The possibility that the effect of trypsin upon serum protein was responsible for the crystals was considered, but couldn't be experimentally proven.
10	60 M Cauc.	Erythremic Myelosis?	Fatigue, weight loss, low grade fever of 4 weeks' duration. Except for pallor, physical examination was	Trace	Hb.: 9 gm. Ht.: 29% Reticulocytes: 18,000 per c.mm.	

			unrevealing. During the 6 months after diagnosis, patient's anemia has worsened and patient requires 4 blood transfusions a month.		(0.6%). Platelets: 350,000. WBC: 6,400. 36 polys, 12 bands, 50 lymphs., 2 nucleated red cells. Anisocytosis 4+ Macrocytosis 2+ Hyperchromia 1+ Targeting 1+. Bone Marrow: Bizarre erythropoiesis.	
11	64 M Cauc.	Dermatomyositis	Diagnosis of dermatomyositis had been made several months prior to admission. Severe malaise, Raynaud's phenomenon.	Trace	Glob.: 5 gm. Hb.: 10 gm. L.E. Tests: negative.	Patient left hospital against medical advice and could not be followed.
12	55 M Cauc.	Rheumatoid Arthritis. Diabetes Mellitus, mild	Thrombosis of retinal artery 2 years prior to admission. Fatigue, arthralgia of several months' duration. 6 months after initial examination, rheumatoid arthritis developed.	Trace	Glob.: 4.8 L.E. Tests: negative. Fasting Blood Sugar: 109 mg.% CBC: Normal.	In this patient the demonstration of hyper- and cryoglobulinemia preceded the development of rheumatoid arthritis by 6 months.
13	60 M N	Carcinoma of esophagus	Gradual development of symptoms of esophageal obstruction. Death after 9 months.	5	Glob.: 2.8 gm.%	Precipitation of cryoglobulin occurred at room temperature.
14	32 M Cauc.	Alcoholic Cirrhosis with jaundice. Severe alcoholism.	Rapid subsidence of jaundice following dietetic therapy.	Trace	Glob.: 4.1 gm.%	Cryoglobulin disappeared with clinical improvement.

ing amounts when tested in the traditional way. The cryocrit varied from a small trace to 30 mm. (Wintrobe tube). The clinical findings of these patients with cryoglobulinemia are summarized in Table 1. Neither crystals nor cold-precipitates were demonstrated in the other patients or normals.

abundant (Table 2). Intracellular crystals appeared regularly when after removal from the refrigerator, the mixture was incubated at 37° C. (Table 2). Moreover, when slides were prepared following incubation of the leukocyte-serum suspension at 37° C. without prior refrigeration, only intracellular crystals were found. Refrigeration following incubation at 37° C. produced an increase of extracellular and in one case also of intracellular crystals, but at no time were intracellular crystals observed without a period of incubation at 37° C.

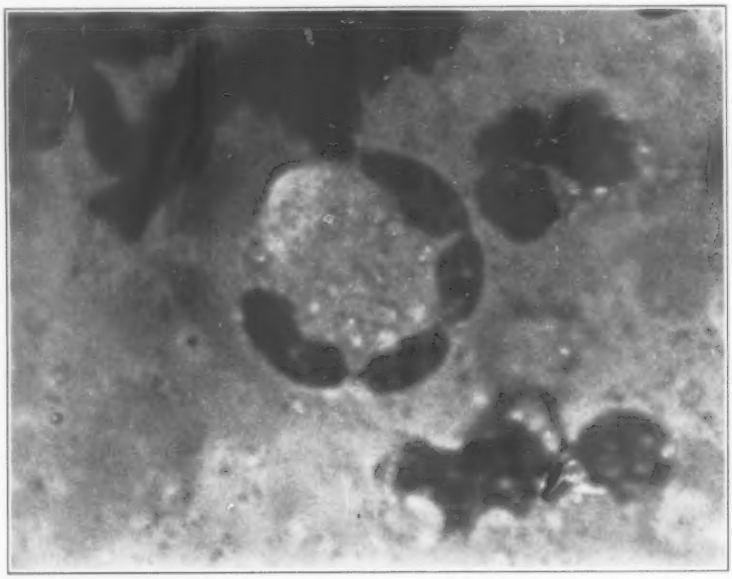


Fig. 1.—Cryoglobulin inclusion cell with homogenous inclusion body. Within the inclusion body there is a crystal.

TABLE 2.—DEPENDENCE OF INTRACELLULAR CRYSTALLIZATION ON TEMPERATURE

Aliquot	*Temperature First Hour, °C.*	*Temperature Second Hour, °C.*	*Crystals*
A_1	5°	5°	Only extracellular
A_2	5°	37°	Predominantly intracellular
B_1	37°	37°	Predominantly intracellular
B_2	37°	5°	Intra- and extracellular

When leukocytes and cryoglobulin containing serum were mixed after both had been maintained at 5° C. for 20 minutes and smears from the buffy layer of the mixture prepared following 1 to 2 hours further refrigeration, intracellular crystals were completely absent, but extracellular crystals were

The possibility that the crystals were

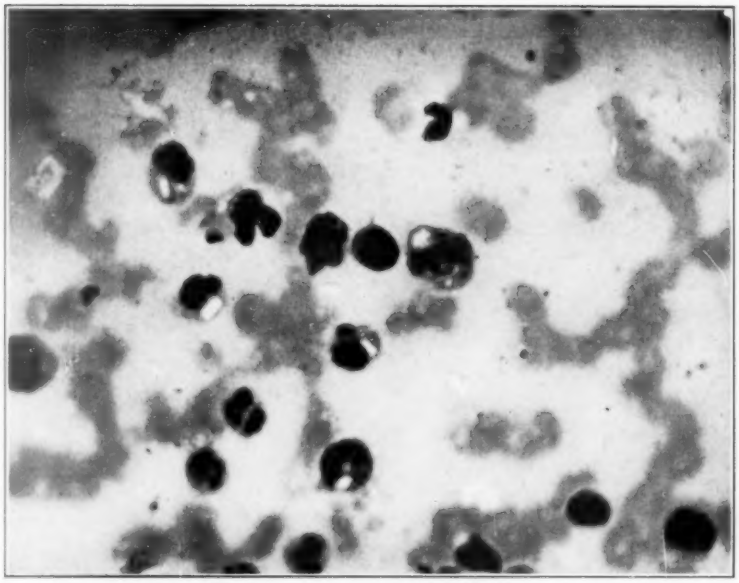


Fig. 2.—Intracellular and extracellular crystals.

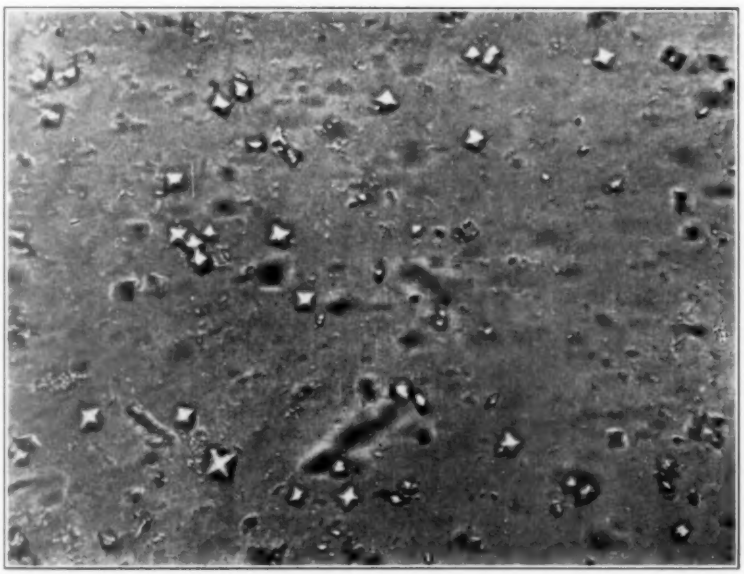


Fig. 3.—Cryoglobulin crystals, precipitated from serum of patient No. 5 (multiple myeloma).

not intracellularly located, but only attached to the surface of the cells was considered. The buffy layer, therefore, was washed 6 times with warm saline following incubation with a cryoglobulin containing serum. The intracellular crystals were found to remain unchanged. When the buffy layer of an aliquot, which had been exposed only to 5° C. was washed, neither intra- nor extracellular crystals were seen after the washing, but in one serum (Pat. 3, Table 1), abundant intracellular crystals were observed following this procedure. This unexpected phenomenon is best explained by the assumption that the few minutes of exposure to warm saline during the manipulation of the preparation were sufficient for phagocytosis and intracellular crystallization to take place before the protein was washed away. In another instance the cryoglobulin precipitated from the serum readily at room temperature and was completely soluble at 37° C., but incubation of the cell-serum mixture at 25° C., yielded very few intracellular crystals while incubation at 37° was followed by a large number of crystals within the cells. These observations seem to indicate that the phenomenon of intracellular crystals is not brought about by phagocytosis of extracellular crystals, but by the crystallization of the phagocytized protein particles within the cytoplasm of the phagocytizing leukocyte.

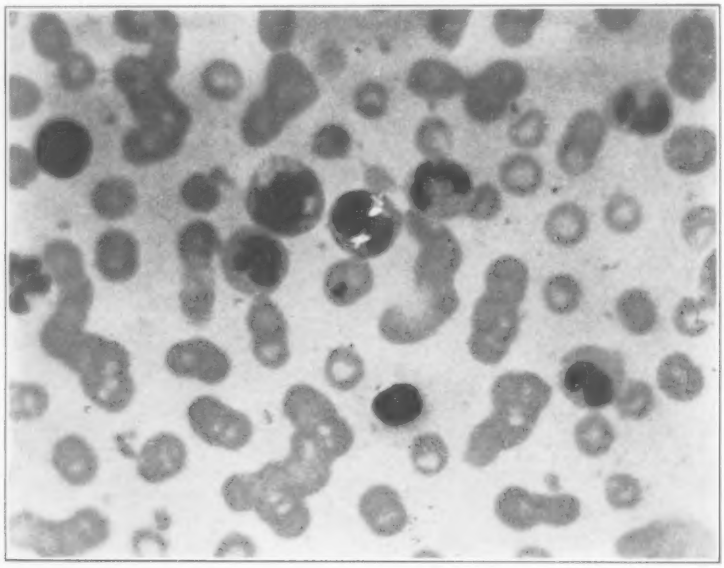


Fig. 4.—"Crystal-inclusion cells."

The close correlation between the presence of intracellular crystals and a cold-precipitate in the serum permitted the preliminary conclusion that the crystallized intracellular particles were of protein character. Supporting this assumption was the fact that the morphologic features of the intracellular crystals and their optic characteristics in the polarizing microscope were identical with those of the extracellular ones (Figs. 3 and 4). The latter could be

proven to be gamma-globulin whenever the amount of precipitate was sufficient for the preparation of a solution for electrophoresis (Fig. 5). The crystals were birefringent and the precipitated in the cold, and in one case of polycythemia even small intracellular inclusion bodies which were not birefringent could be demonstrated. It is possible that the plasma of

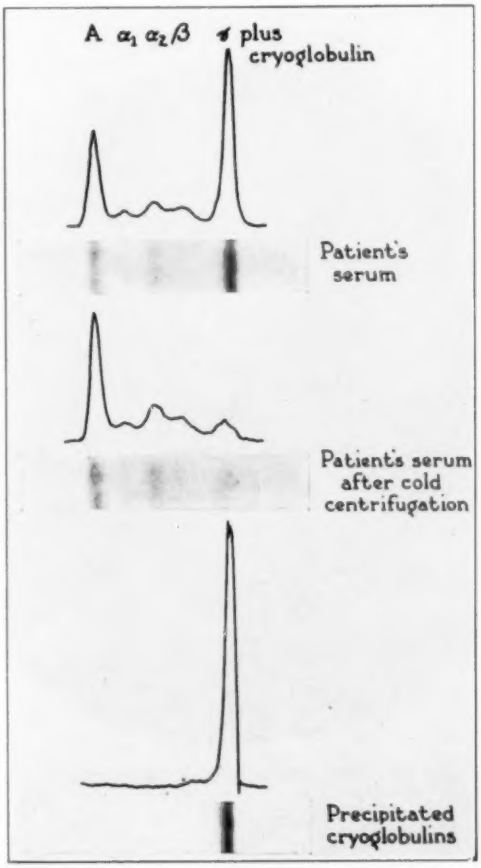

A α_1 α_2 β γ plus cryoglobulin
Patient's serum
Patient's serum after cold centrifugation
Precipitated cryoglobulins

Fig. 5.—Paper electrophoresis of cryoglobulin from serum of patient with multiple myeloma. The largest part of the myeloma-gamma-protein was precipitated by cold. The high peak in the electrophoretogram is caused by the higher concentration of cryoglobulin in the solution than in the serum.

angle of extinction was 90° (± 5°) for all crystals (Figs. 3 and 4).

In the initial phase of this study, not only serum, but also oxalate-plasma and heparin-plasma were incubated with leukocytes. This was later abandoned because fibrinogen occasionally was this patient contained a cryofibrinogen (Korse and Kratochvil[21]). The serum was free of cryoglobulin. When oxalate plasma was used, large needle-like or oval oxalate crystals were occasionally observed. Although they could hardly be confused with cryoglobulin crystals,

the possibility of such artefacts made it advisable to use only serum.

For the immunological characterization of the intracellular crystals, the Ouchterlony plates were prepared in the following way: In the first (Fig. 6) rabbit serum, containing antibodies to human serum ("Anti-Human Serum") was allowed to react with a cryoglobulin serum; a solution of the cold-precipitate in saline; the supernatant serum; and denatured protein. All substances reacted strongly with the anti-human serum, except for the denatured protein, which reacted only slightly. The single precipitation line between the anti-human serum and the cryoglobulin indicated the immunologic homogeneity of the cryoglobulin solution as compared to the whole serum and the supernatant serum, which contained a mixture of antigenic groups. In another Ouchterlony plate (Fig. 7), again anti-human serum was the antibody, but the following preparations were used as antigens: (a) lysate of washed leukocytes, (b) lysate of washed leukocytes which had

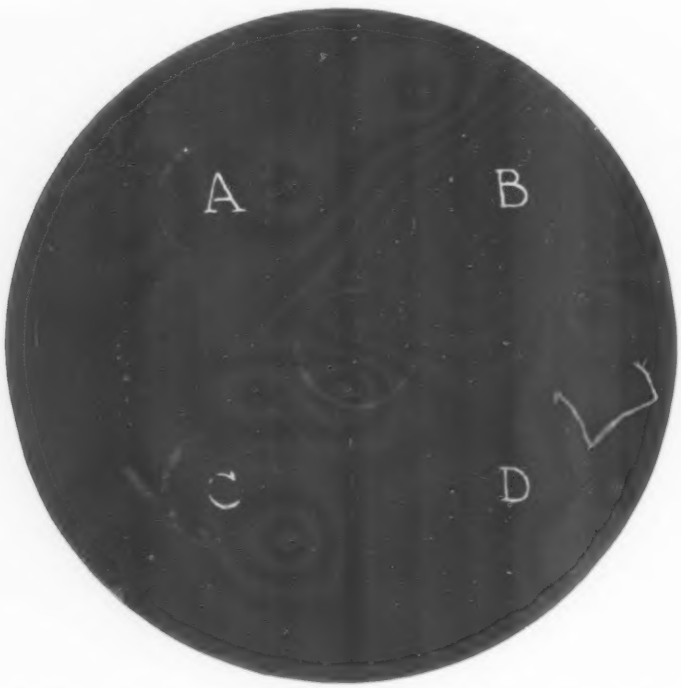


Fig. 6.—Ouchterlony Plate. In center well is "anti-human serum" (Serum from rabbits sensitized with human serum).

A. Whole serum containing cryoglobulin
B. Solution of separated cryoglobulin
C. Supernatant of serum after removal of precipitated cryoglobulin
D. Denatured protein

Note 3 precipitation zones between center well and A and C, while there is one line between the center well and B. The merging of the lines of the corners indicates complete immunologic similarity.

been previously incubated with a cryoglobulin serum and were shown to contain crystals, (c) lysate of washed leukocytes which had been previously incubated with normal serum and did not contain any crystals, (d) lysate of washed leukocytes incubated with debated with normal serum seemed to indicate that no protein particles of normal serum were phagocytized, whereas this had occurred with the cryoglobulin. A denatured serum protein was chosen as fourth antigen because of its insolubility, in this respect

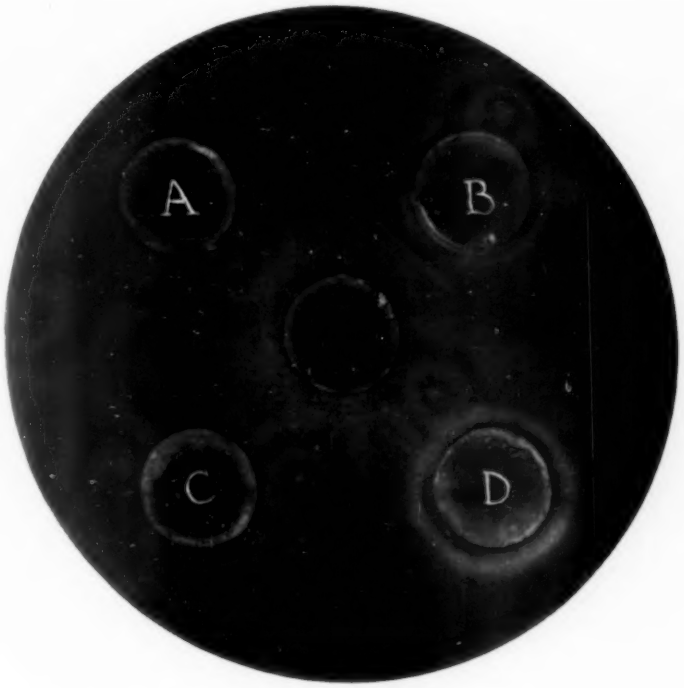


Fig. 7.—Ouchterlony Plate. Center well: anti-human serum.
A. Lysate of washed white cells previously incubated with denatured protein.
B. Lysate of washed leukocytes previously incubated with a cryoglobulin serum.
C. Lysate of washed leukocytes previously incubated with normal serum.
D. Lysate of washed leukocytes.
Note single precipitation band between center well and B.

natured serum protein. Lysis of the leukocytes following phagocytosis was expected to release antigenic protein. As predicted a single precipitation line was seen between the lysate of washed leukocytes containing the crystals and the anti-human serum. The absence of a line between the latter and the lysate of washed cells previously incuresembling the cryoglobulin. This denatured protein reacted only slightly in the free state and either was not phagocytized by the leukocytes from which it could be completely removed by washing, or if phagocytosis occurred, its antigenicity was not strong enough for the formation of a demonstrable precipitate.

Although it would have been of interest to produce an antigen to cryoglobulin itself and study cross reactions with other cryoglobulins, this did not appear to be relevant to this investigation, the purpose of which, was the determination of the nature of the intracellular crystals, and the mechanism of their production. The fact that the anti-human serum was found to form a precipitation zone with the cryoglobulin was interpreted as lack of complete immunologic specificity of the cryoglobulin which contains antigenic groups also present in normal serum. This had previously been demonstrated by Korngold and Lipari[19] and by Rice[41] for myeloma cryoglobulins.

Ultracentrifugal analysis of the serum from one patient confirmed the diagnosis of "essential macroglobulinemia" (Waldenstrom[52]) which was suspected on the basis of clinical findings and the spontaneous gelling of the serum at room temperature. The ultracentrifugal demonstration of proteins with high molecular weight sedimenting with Svedberg constants of more than 15 S and in concentration greater than 5% is considered essential to the diagnosis of macroglobulinemia (Braunsteiner[5], Mackay *et al.*[26] and Waldenstrom[52]). This is frequently associated with cryoglobulinemia (Mackay *et al.*[26], Mandema, Vander Schaaf and Huisman[27] and Peterman and Braunsteiner[37]), as it was the case in the patient of this report (Case No. 2, Table 1).

Discussion. Cryoglobulins have been found in many diseases associated with abnormalities of the reticuloendothelial system. These abnormalities are either reactive as in subacute bacterial endocarditis (Dreyfuss and Librach[8], and Wertheimer and Stein[53]), Kala-Azar (Most and Lavietes[30]), cirrhosis of the liver (Barr, Reader and Wheeler[3], Braunsteiner *et al.*[5], and Wertheimer and Stein[53]) and the group of diseases usually classified as collagen diseases (Barr, Reader and Wheeler[3], Butler and Palmer[6], Lepow *et al.*[23] and Shapiro and Wertheimer[44]); or they are manifestations of malignant disease, as in lymphatic leukemia (Craig, Waterhouse and Young[7], and Schwartz and Jager[43]), lymphosarcoma (Abrams, Cohen and Meyer[1], Griffith *et al.*[11], Griffith and Gilchrist[12], and Shaw[45]), carcinoma (Bohrod[4]), or multiple myeloma (Barr, Reader and Wheeler[3], Engle and Wallis[9], Fitzgerald, Cantwell and McCarthy[10], Hill, Dunlop and Mulligan[15], Marshall and Malone[28], Nelson and Neill[32], Rorvik[42], Wintrobe and Buell[55]), the latter being the most common cause of cryoglobulinemia. Korse and Kratochvil[21] made the interesting observation of a cryofibrinogen in a patient with carcinoma of the pancreas and considered it a possible cause of the migratory thrombophlebitis frequently associated with this tumor. There have been occasional case reports (Barr, Engle and Russ[2], Barr, Reader and Wheeler[3], Gunz[13], Lerner and Watson[24], Mackay *et al.*[26], Muirhead, Montgomery and Gordon[31], Steinhardt and Fisher[48], Volpe *et al.*[50], Volpe and Ogryzlo[51]) about patients in whom cryoglobulinemia appeared to be the sole basic pathologic feature considered to be responsible for the clinical-pathological manifestations; for example, cold urticaria, purpura, progressive deafness, Raynaud's phenomenon and visceral infarctions. The predominance and intensity of any of these symptoms may vary. Amputation of extremities may become necessary (Barr, Reader and Wheeler[3], Hutchinson and Howell[16]) as it was the case in our patient with this syndrome. For want of knowledge of its cause, this syndrome has been designated as "essential cryoglobulinemia" (Volpe *et al.*[50,51]).

Usually only the patients, whose serum contains high cryoglobulin levels, manifest symptoms attributable to the cryoglobulin. In only occasional reported cases, characteristic symptoms were present although the concentration of cryoglobulin was small (Barr, Engle and Russ[2], Mackay *et al.*[26], Wertheimer and Stein[53]), but in the absence of such symptoms, no clinical significance has been attributed to such small amounts of cryoglobulin by investigators who have examined a large number of patients with various diseases (Barr, Engle and Russ[2], James and Drake[17], Lerner, Barnum and Watson[25]). It should be emphasized, however, that the majority of these diseases belong to the previously listed groups. In the report of Barr, Reader and Wheeler[3], the 16 patients whose serum contained a small amount of cryoglobulin suffered from disseminated lupus erythematosus, Raynaud's disease, Buerger's disease, multiple myeloma, lymphogranuloma venereum, chronic hepatitis, pneumonia, myocarditis, Hodgkin's disease, and alcoholism. A similar array of diseases had been enumerated in the report of Lerner, Barnum and Watson[25], including subacute bacterial endocarditis and rheumatic fever. The diseases of the patients of the present report are of similar nature. The frequency of cryoglobulinemia in subacute bacterial endocarditis has been stressed by Wertheimer and Stein[53] and more recently by Dreyfuss and Librach[8]. It is of interest that in one of our patients, the demonstration of intracellular crystals, routinely searched for in the course of this study, was the earliest available laboratory confirmation of the clinically suspected diagnosis of subacute bacterial endocarditis.

James and Drake[17] have claimed to have found traces of cryoglobulin in 40% of 69 patients with coronary artery disease and in the absence of increased viscosity of the serum have not attributed any clinical significance to this finding. To our knowledge, no other report on this phenomenon in patients with coronary artery disease is available. Because of the possible pathogenetic implications of this biochemical abnormality, we were interested in this finding, but have been unable to confirm it.

There appears to be no doubt that the presence of a large amount of cryoglobulin is indicative of a severe derangement of protein production, and most investigators agree that even traces of cryoglobulin are absent from normal serum. It might, therefore, not be justified to deny any pathological significance to the presence of such small amounts in the serum, especially if there is some pattern in their occurrence. Occasionally, the demonstration of a trace of cryoglobulin may even be a practical diagnostic aid when the diagnosis of a disease is not yet established and any additional clue carries valuable weight.

Spontaneous crystallization of a protein from serum is a rare phenomenon. This has only been found to occur with cryoglobulins (Lerner and Watson[24], Putnam[40], and Shapiro and Wertheimer[44]) and macroglobulins (Kratochvil[22]). The temperature at which precipitation and crystallization occur varies from one cryoglobulin to the other, as do other physicochemical characteristics. Some may precipitate only at temperatures close to the freezing point, others may start to precipitate even at room temperature. It also is a well established fact that the optimal temperature of precipitation depends on the concentration of the cryoglobulin (Volpe *et al.*[50]). The higher the concentration, the likelier precipitation and even crystallization occur at higher temperature. These

facts can serve as an explanation for the appearance of clinical manifestations of vascular occlusion or purpura without exposure to cold. At lower concentration of the cryoglobulin, the precipitation temperature may not only be below 5° C., but also the exposure of the serum sample may have to be prolonged before maximal precipitation occurs. Lerner, Barnum and Watson[25] observed occasional precipitates after 7 days of exposure of the serum to cold. This temperature-concentration relationship may also be an important factor in the described phenomenon of intracellular crystals. As intracellular crystals are only demonstrable following incubation of the serum with leukocytes at 37° C., the leukocytes most likely phagocytize the cryoglobulin in the uncrystallized state. The subsequently increasing concentration within the cell, and perhaps other unexplored physicochemical factors probably lead to saturation and to precipitation at the incubation temperature.

Intracellular crystals have been found in various organs (Engle and Wallis[9], Neumann[33], Sikl[46] and Valach[49]) at necropsy of myeloma patients, especially in the bone marrow and in the renal tubular cells. The substance of these crystals and the mechanism of their formation is not known, but it is likely that they are of protein nature. Since the pathological proteins of multiple myeloma may have the characteristics of a cryoglobulin, it is possible that the mechanism of intracellular crystal formation is similar to the one proposed in this report.

The immunologic experiments of this study have shown that the crystals are truly intracellular and react with anti-human rabbit serum. The lysate of leukocytes which had been exposed to normal serum and the lysate of leukocytes with the inclusion crystals differed in their immunologic reaction with hyperimmune serum. This reaction appears to depend solely on the phagocytized globulin thus not only proving the protein nature of the crystals, but also their intracellular position prior to the preparation of the lysate. Slater, Ward, and Kunkel[47]; Korngold and Lipari[19], and Rice[41] have shown that immunologically the cryoglobulins of multiple myeloma are related to normal gamma-globulin. This fact explains the strong precipitation reaction of cryoglobulin with a hyperimmune anti-human serum, as demonstrated on the Ouchterlony plates of this study.

The possibility that the cryoglobulins themselves are the product of an immunologic process has been suggested by Volpe and his co-workers[50]. These authors noted a high anticomplementary titer of the cryoglobulinemic serum and disappearance of the low solubility of such a serum following inactivation of complement. They speculated that the instability of cryoglobulins was caused by a labile immunologic complex of gamma-globulin and beta-lipoproteins which requires complement. Since addition of guinea pig complement did not restore the property of cold-precipitation in Volpe's experiment, it is possible that this postulated reaction requires properdine (Pillemer, Blum and Lepow[38]). We have attempted to reproduce Volpe's findings with the intention to test the effect of properdine, but were not able to "inactivate" our cryoglobulin sera. Neither crystallization nor phagocytosis of the cryoglobulin was inhibited by heating of the serum to 56° for 30 minutes.

The phenomenon of the crystal inclusion cell can be utilized for a sensitive and apparently specific diagnostic test for cryoglobulinemia. It is recommended that clotted blood be incu-

bated at 37° for 1 hour and exposed to 5° C. for an additional hour. Thereafter, the smears are prepared according to the method of Zimmer and Hargraves[56]. The additional hour of refrigeration is not essential, but considered advisable because of the occasional enhancement of intracellular crystallization at this temperature.

Summary and Conclusion. 1. Intraleukocytic crystals have been observed in the L.E. cell preparation of patients with cryoglobulinemia.

2. These crystals can only be seen when the leukocytes and the serum are incubated at 37° C. This phenomenon has been interpreted as being the result of phagocytosis of uncrystallized cryoglobulin followed by intracellular crystallization.

3. The protein nature of the crystals is suggested by the results of the immunologic studies.

4. This phenomenon can be utilized for a sensitive and apparently specific test for the demonstration of small amounts of cryoglobulin.

5. The pathological and clinical significance of mild asymptomatic cryoglobulinemia is not clearly established, but its occurrence appears to be related to disorders of the reticuloendothelial system. It is hoped that with the aid of a simple test as the one described in this study, the clinical significance of cryoglobulins will be further clarified.

ACKNOWLEDGMENTS: We are grateful to Mr. Charles W. Hoerr, Armour Research Division, for valuable advice in the crystal analysis, to Dr. Norman Frank, Clarendon Hills, Illinois, for referral of the patient with essential macroglobulinemia, to Mr. Lemuel Hall for technical assistance and to the Medical Illustration Service, V.A. Westside Hospital, for the excellent photographic work.

REFERENCES

1. **Abrams, A., Cohen, P. P.,** and **Meyer, O. O.:** J. Biol. Chem., **181,** 237, 1949.
2. **Barr, D. P., Engle, R. L.,** and **Russ, E. M.:** Ann. Int. Med., **47,** 1225, 1957.
3. **Barr, D. P., Reader, G. G.,** and **Wheeler, C. H.:** Ibid., **32,** 6, 1950.
4. **Bohrod, M. G.:** J. Am. Med. Assn., **164,** 18, 1957.
5. **Braunsteiner, H., Falkner, R., Neumayer, A.,** and **Pakesch, F.:** Klin. Wchnschr., **32,** 722, 1954.
6. **Butler, K. R.,** and **Palmer, J. A.:** Canad. Med. Assn. J., **72,** 686, 1955.
7. **Craig, A. B., Waterhouse, C.,** and **Young, L. E.:** Am. J. Med., **13,** 793, 1952.
8. **Dreyfuss, F.,** and **Librach, G.:** J. Lab. & Clin. Med., **40,** 489, 1952.
9. **Engle, R. L.,** and **Wallis, L. A.:** Am. J. Med., **22,** 5, 1957.
10. **Fitzgerald, O., Cantwell, D.,** and **McCarthy, E.:** Irish J. Med. Sci., **6,** 1. 1956.
11. **Griffith, L. L., Gilchrist, L., King, M. B.,** and **Brews, V. A. L.:** Lancet, **2,** 1286, 1954.
12. **Griffith, L. L.,** and **Gilchrist, L.:** Lancet, **1,** 882, 1953.
13. **Gunz, F. W.:** Brit. J. Haem., **2,** 95, 1956.
14. **Hardy, S.,** and **Putnam, F. W.:** J. Biol. Chem., **212,** 371, 1955.
15. **Hill, R. M., Dunlop, S. G.,** and **Mulligan, R.:** J. Lab. & Clin. Med., **34,** 1056, 1949.
16. **Hutchinson, J. H.,** and **Howell, R. A.:** Ann. Int. Med., **39,** 350, 1953.
17. **James, T. N.,** and **Drake, E. H.:** New England J. Med., **249,** 601, 1953.
18. **Korngold, L.:** J. Immun., **77,** 119, 1956.
19. **Korngold, L.,** and **Lipari, R.:** Cancer, **9,** 183, 1956.
20. **Korngold, L.,** and **Van Leeuwen, G.:** J. Exper. Med., **106,** 467, 1957.
21. **Korse, D. R.,** and **Kratochvil, C. H.:** Blood, **10,** 945, 1955.
22. **Kratochvil, C. H.,** and **Deutsch, H. F.:** J. Biol. Chem., **222,** 31, 1956.
23. **Lepow, M., Rubenstein, L., Voll, F.,** and **Greisman M.:** Am. J. Med. Sci., **214,** 416, 1947.
24. **Lerner, A. B.,** and **Watson, C. J.:** Ibid., **214,** 410, 1947.
25. **Lerner, A. B., Barnum, C. P.,** and **Watson, C. J.:** Ibid., **214,** 416, 1947.

26. **Mackay, I. R., Ericksen, N., Motulsky, A. G.,** and **Volwiler, W.:** Am. J. Med., **20,** 564, 1956.
27. **Mandema, E., Vander Schaaf, P. C.,** and **Huisman, T. M. J.:** J. Lab. & Clin. Med., **45,** 261, 1955.
28. **Marshall, R. J.,** and **Malone, R. G. S.:** Brit. Med. J., **2,** 279, 1954.
29. **Morrison, P. R., Edsall, J. T.,** and **Miller, J. G.:** J. Am. Chem. Soc., **20,** 3103, 1948.
30. **Most, H.,** and **Lavietes, P. H.:** Medicine, **26,** 221, 1947.
31. **Muirhead, Z. Z., Montgomery, P. O. B.,** and **Gordon, C. E.:** A.M.A. Arch. Int. Med., **89.** 41. 1952.
32. **Nelson, M. G.,** and **Neill, D. W.:** Irish J. Med. Sci., **6,** 271, 1955.
33. **Neumann, V.:** J. Path. & Bact., **61,** 165, 1949.
34. **Olhagen, B.:** Acta med. Scandinav., (Suppl.), **239,** 86, 1950.
35. **Ouchterlony, O.:** Acta path. microbiol. Scandinav., **26,** 507, 1949.
36. Idem: Ibid., **32,** 231, 1953.
37. **Peterman, M. L.,** and **Braunsteiner, M.:** Arch. Bioch. Biophys., **53,** 491, 1954.
38. **Pillemer, L., Blum, L.,** and **Lepow, I. M.:** Science, **120,** 279, 1954.
39. **Putnam, F. W.,** and **Miyake, A.:** Arch. Bioch. Biophys., **65,** 39, 1956.
40. **Putnam, F. W.:** Phys. Reviews, **37,** 512, 1957.
41. **Rice, W. G.:** Lab. Invest., **5,** 410, 1956.
42. **Rorvik, K.:** Acta med. Scandinav., **137,** 390, 1950.
43. **Schwartz, T. B.,** and **Jager, B. V.:** Cancer, **2,** 319, 1949.
44. **Shapiro, B.,** and **Wertheimer, E.:** Brit. J. Exper. Path., **27,** 225, 1946.
45. **Shaw, A. B.:** Proc. Royal Soc. Med., **49,** 115, 1956.
46. **Sikl, H.:** J. Path. & Bact., **61,** 149, 1949.
47. **Slater, R. J., Ward, S. M.,** and **Kunkel, H. G.:** J. Exper. Med., **101,** 85, 1955.
48. **Steinhardt, M. J.,** and **Fisher, G. S.:** J. Allergy, **24,** 335, 1953.
49. **Valach, V.:** Schweiz. Ztschr. Path. Bakt., **20,** 383, 1957.
50. **Volpe, R., Bruce-Robertson, A., Fletcher, A. A.,** and **Charles, W. B.:** Am. J. Med., **20,** 533, 1956.
51. **Volpe, R.,** and **Ogryzlo, M. A.:** Blood, **10,** 493, 1955.
52. **Waldenstrom, J.:** Adv. in Int. Med., **5,** 398, 1952.
53. **Wertheimer, E.,** and **Stein, L.:** J. Lab. & Clin. Med., **29,** 1082, 1944.
54. **Westendorp, F.,** nd **Mandema, E.:** Ibid., **49,** 358, 1957.
55. **Wintrobe, M. M.,** and **Buell, M. V.:** Bull. Johns Hopkins Hosp., **52,** 156, 1933.
56. **Zimmer, F. E.,** and **Hargraves, M. M.:** Proc. Staff Meet., Mayo Clin., **27,** 424, 1952.

(Interlingua on page 203)

THE OXYHEMOGLOBIN DISSOCIATION CURVE IN SICKLE CELL ANEMIA

By William Fraimow, M.D.
FORMER RESIDENT IN MEDICINE

Theodore Rodman, M.D.
STAFF PHYSICIAN

Henry P. Close, M.D.
CHIEF, MEDICAL SERVICE

Richard Cathcart, M.D.
CONSULTANT IN PULMONARY PHYSIOLOGY

AND

May K. Purcell
CHIEF CARDIOPULMONARY FUNCTION TECHNICIAN

(From the Medical Service and Cardiopulmonary Function Laboratory, Veterans Administration Hospital, Philadelphia, Pennsylvania)

A high incidence of arterial oxygen unsaturation has been reported in sickle cell anemia (Becklake *et al.*[2], Fowler, Smith and Greenfield[5], Fowler, Westcott and Scott[6], Jensen, Rucknagel and Taylor[7], Leicht *et al.*[9], Moser and Shea[10], Reinhard *et al.*[13], Scriver and Waugh[18], Sproule, Halden and Miller[19], and Tinsley *et al.*[20]). This unsaturation has been attributed both to the pulmonary complications of the sicklemic state and to the presence of the abnormal hemoglobin itself.

In the presence of a normal alveolar oxygen tension there are 3 physiologic abnormalities which can result in arterial oxygen unsaturation. These are a reduction in diffusion capacity, an increased admixture of venous blood into the arterial circulation, and a shift of the oxyhemoglobin dissociation curve to the right and downward. Each of these potential mechanisms has been implicated by various investigators. In addition, arterial oxygen unsaturation has been reported in other anemic states (Kennedy and Valtis[8], and Ryan and Hickam[16]), and might, therefore, be a complication of the low hemoglobin level rather than the sickle cell disease.

Moser and Shea[10] suggested that repeated occlusions of pulmonary vessels produced a reduction in the diffusion surface of the pulmonary capillary bed. Sproule, Halden and Miller[19] have recently reported data which indicate that the unsaturation is due to increased venous admixture. Becklake and his associates[2], using *in vitro* techniques, demonstrated displacement of the oxyhemoglobin dissociation curve. Using both *in vitro* and *in vivo* techniques Fowler[5] has demonstrated both a displacement of the dissociation curve and an increase in the alveolar-arterial oxygen tension gradient.

Three patients with sickle cell disease who had arterial oxygen unsaturation were studied in an attempt to clarify the etiology of the unsaturation. In addition to the usual tests of ventilation, distribution, and diffusion, the physiologic oxygen dissociation curves

were plotted by allowing the patients to breathe various mixtures of oxygen and nitrogen and determining both the saturation and the oxygen tension of the arterial blood.

Methods and Materials. The clinical diagnosis of sickle cell anemia was confirmed by electrophoretic and alkali denaturation studies of the hemoglobin. The initial hemoglobin level varied between 6.8 and 9.9 gm. per 100 ml. None of the 3 patients had received a recent transfusion. All had been free of clinical episodes of pulmonary infarction and pneumonitis.

The vital capacity, maximum breathing capacity, and timed vital capacity were measured with a 13.5 liter Collins respirometer. The index of intrapulmonary mixing and functional residual capacity was measured in duplicate by the open circuit oxygen inhalation method (Baldwin, Cournand and Richards[1]). The expired air was collected in a 125 liter Tissot gasometer and analyzed with a Waters nitrogen gas analyzer. Expired gases were analyzed for O_2 and CO_2 by the micro-Scholander technique[17]. Duplicates were required to check within .03%. Arterial blood was obtained through an indwelling Cournand needle placed in the brachial artery and analyzed for oxygen content, oxygen capacity, and CO_2 content using the Van Slyke and Neill manometric apparatus[11]. Duplicates were required to check within .022 ml. per 100 ml. for oxygen and within .4 ml. per 100 ml. for CO_2. CO_2 tensions were calculated from the line charts of Van Slyke and Sendroy[21], and the Henderson-Hasselbach equation. Arterial oxygen tensions were measured directly by the bubble equilibration technique of Riley, Proemmel, and Franke[15] using 50 mm. capillaries with a 0.5 mm. bore fused to tuberculin syringes. Equilibrations were carried out in a constant temperature water bath maintained at 37° C. ± 0.2°. Duplicate determinations were required to check within 5 mm. Hg. Arterial pH was measured at 37° C. with a Cambridge electron-ray research model pH meter. Alveolar oxygen tensions were calculated on the basis of the alveolar gas equation. In order to plot the oxyhemoglobin dissociation curve each patient was studied twice, usually on consecutive days. Three or four points on the dissociation curve were obtained each day. A steady state was obtained by permitting the patient to breathe each gas mixture for 25 to 30 minutes before arterial blood samples and expired air were collected.

Results. Table 1 shows that no major aberration in pulmonary function was demonstrated except for the arterial oxygen unsaturation. The slight reduction in vital capacity might be attributed to the asthenic habitus of these patients or to mild restrictive changes. In all 3 patients, while breathing ambient air, there was marked arterial oxygen unsaturation but normal pH, CO_2 content, and CO_2 tension.

TABLE 1.—PULMONARY FUNCTION STUDIES

	D.B.	*E.Y.*	*J.J.*
Ventilation L/min./M^2	4.78	3.25	3.74
VC % predicted	82	72	72
Three second timed VC % observed	100	100	93
MBC L/min.	123	91	93
Total lung capacity, L.	4.91	3.80	4.47
Residual volume, L.	1.39	.795	1.17
RV/TLC × 100	28	21	26
Arterial O_2 saturation			
Rest	83.3	80.7	88.4
Exercise	85.8	76.8	84.7
Arterial CO_2 tension mm. Hg	40	41	38
Pulmonary mixing index	1.2	2	1.6

To evaluate the possibility of a reduction in diffusion capacity or an increased venous admixture, alveolar-arterial oxygen gradients were measured with the patient breathing 2 different mixtures of oxygen and nitrogen. The data are tabulated in Table 2. The gradients are within normal limits and suggest that in these 3 patients neither diffusion difficulties nor increased venous admixture are responsible for the arterial oxygen unsaturation.

A portion of the oxyhemoglobin dissociation curve was then determined for each patient. Table 3 shows the data for patient D.B. Six points on the

O_2 dissociation curve were determined on arterial blood during the administration of the indicated concentration of oxygen. The lowest oxygen tension obtained was 77 mm. Hg with a saturation of 75.5% and the highest 125 mm. Hg with a saturation of 90.8%. An additional point on the dissociation curve was obtained from venous blood which had an oxygen tension of 60 mm. Hg and a saturation of 55.9%. These points are plotted in Fig. 1 and a dissociation curve is projected from them, which is compared with the normal curve at pH 7.40. It can be seen that patient D.B.'s curve, although normal in configuration, falls far to the right of the normal curve so that at any given oxygen tension there is significantly less oxygen saturation of the hemoglobin.

In a similar manner a curve was constructed for patient J.J. from 6 arterial

TABLE 2.—ALVEOLAR ARTERIAL OXYGEN GRADIENT STUDIES

	Inspired Air O_2 %	*Alv. pO_2 mm. Hg*	*Art. pO_2 mm. Hg*	*A–a O_2 Gradient mm. Hg*	*Art. O_2 Sat. %*
D.B.	20.94	105	91	14	87.5
	17.93	85	77	8	75.5
E.Y.	20.89	97	82	15	89.1
	13.91	54	51	3	64.5
J.J.	20.89	98	85	13	72.4
	17.93	79	68	11	69.2

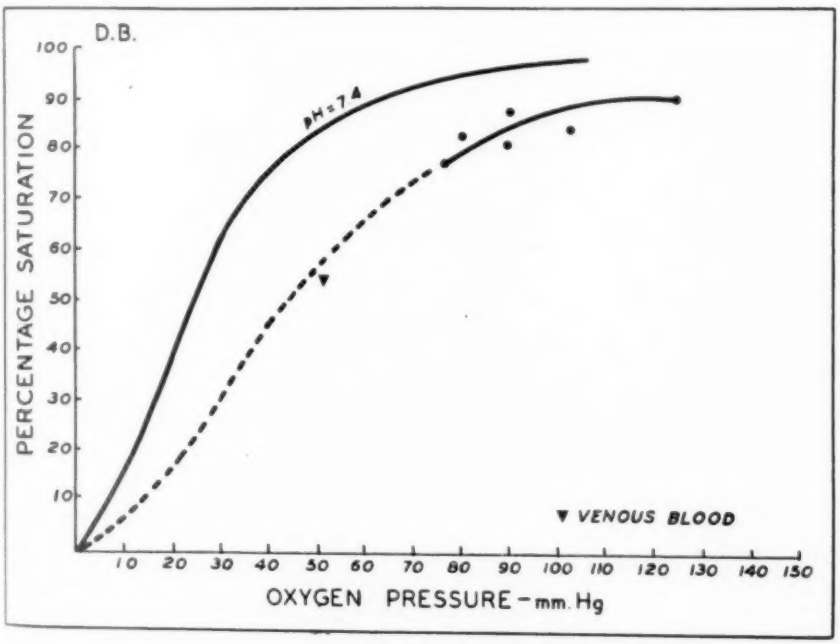


Fig. 1.—Showing 6 points determined on arterial blood and 1 on venous blood of patient D.B. with the dissociation curve projected from these points. No correction for pH which varied between 7.38 and 7.43. Solid black line for the normal curve at pH 7.4 established by Dill.

points. The data are tabulated in Table 4 and plotted in Fig. 2. At an arterial oxygen tension of 127 mm. Hg this patient's hemoglobin was only 84.2% saturated with oxygen.

The data on patient E.Y. are tabulated in Table 5 and plotted in Fig. 3. Seven arterial points were obtained. Although this patient's curve appeared to reach the normal one at higher tensions, it was significantly displaced at lower levels.

In an attempt to evaluate the role played by anemia in the shift of the

TABLE 3.—ARTERIAL BLOOD STUDIES USED IN PLOTTING OXYHEMOGLOBIN DISSOCIATION CURVE FOR PATIENT D.B.

D.B.

Date	Inspired Air O_2 %	Art. pO_2 mm. Hg	pH	Art. O_2 Sat. %
9–23–57	20.95	81	7.43	83.1
	25.49	90	7.38	81.8
	29.35	103	7.40	85.0
9–24–57	17.93	77	7.42	75.5
	20.95	91	7.40	87.5
	39.25	125	7.43	90.8

Hb. 8.5 gm. per 100 ml. S–S Type

TABLE 4.—ARTERIAL BLOOD STUDIES USED IN PLOTTING OXYHEMOGLOBIN DISSOCIATION CURVE FOR PATIENT J.J.

J.J.

Date	Inspired Air O_2 %	Art. pO_2 mm. Hg	pH	Art. O_2 Sat. %
8–14–57	20.89	75	7.47	66.6
	22.60	83	7.44	75.7
	25.49	90	7.43	85.5
8–15–57	29.35	99	7.42	80.4
	33.95	109	7.44	83.7
	38.90	127	7.42	84.2

Hb. 6.8 gm. per 100 ml. S–S Type

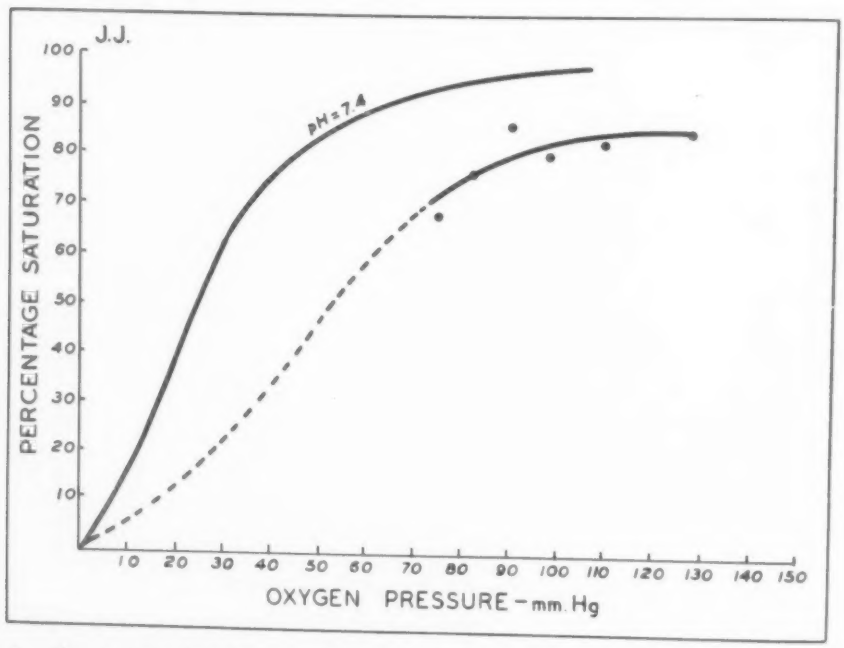


Fig. 2.—Showing 6 points determined on arterial blood of patient J. J. with the dissociation curve projected from them. No correction for pH which varied between 7.42 and 7.47. Solid black line for the normal curve at pH 7.4 established by Dill.

dissociation curve one patient (J.J.) was restudied following the transfusion of 1500 ml. of normal whole blood. The data are tabulated in Table 6 and plotted in Fig. 4 along with the patient's pretransfusion curve and the normal curve. Although the post-transfusion curve is less displaced than the pretransfusion one, it is still markedly shifted when compared with the normal.

TABLE 5.—ARTERIAL BLOOD STUDIES USED IN PLOTTING OXYHEMOGLOBIN DISSOCIATION CURVE FOR PATIENT E.Y.

E.Y.

Date	*Inspired Air* O_2 %	*Art.* pO_2 *mm. Hg*	*pH*	*Art.* O_2 *Sat.* %
10–3–57	17.93	69	7.38	82.8
	20.89	89	7.42	92.1
	22.64	93	7.40	97
	25.49	108	7.41	98.2
10–9–57	13.91	51	7.44	64.5
	16.25	72	7.43	73.4
	20.89	82	7.41	89.1

Hb. 9.9 gm. per 100 ml. S 95.4% F 4.6%

TABLE 6.—ARTERIAL BLOOD STUDIES USED IN PLOTTING POSTTRANSFUSION CURVE FOR PATIENT J.J.

J.J.

Date	*Inspired Air* O_2 %	*Art.* pO_2 *mm. Hg*	*pH*	*Art.* O_2 *Sat.* %
11–4–57	29.35	113	7.42	91.3
	25.49	100	7.40	88.5
	20.89	94	7.39	89.4
11–5–57	58.30	183	7.40	91.4
	16.25	70	7.41	85.0
	13.91	64	7.41	80.2

Hb. 11.5 gm. per 100 ml. S 59.5% A 40.5%

Discussion. Scriver and Waugh[18] in reporting the first case of sickle cell anemia described in Canada stated that the oxyhemoglobin dissociation

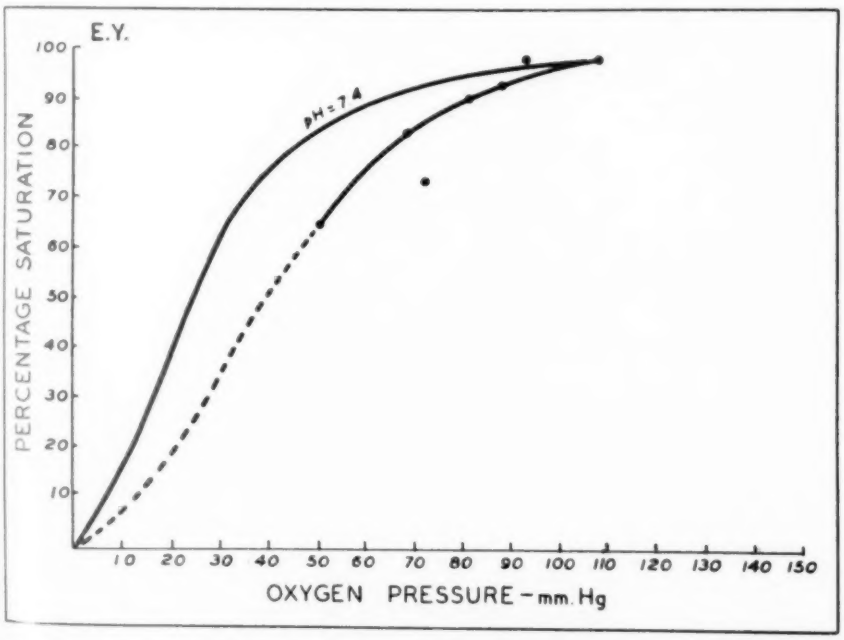


Fig. 3.—Showing 7 points determined on arterial blood for patient E.Y. with the dissociation curve projected from them. No correction for pH which varied between 7.38 and 7.44. Solid black line for the normal curve at pH 7.4 established by Dill.

curve was shifted to the right. They presented no data to corroborate their conclusion. More recently, the same conclusion was reached by Becklake *et al.*[2] using tonometric techniques and Fowler, Smith and Greenfield[5] using both tonometric and *in vivo* techniques. Our observations confirm the presence of an abnormal oxyhemoglobin dissociation curve. By obtaining at least 6 points for each patient we were able to plot a large segment of that patient's curve and demonstrate that the shift can be of considerable magnitude. In 2 of our 3 patients the flat portion of the curve projects at such a level as to preclude the possibility of attaining normal arterial oxygen saturation on inhalation of ambient air. Full saturation of the arterial blood was attained, however, in all 3 patients on inhalation of 100% oxygen. On the basis of our data we feel that, in the 3 patients studied, the shift in the dissociation curve is sufficient to account for the observed arterial oxygen unsaturation regardless of the presence or absence of pulmonary changes. Since the number of patients we have studied is small, we can draw no conclusions regarding the frequency of the change we have described. It is possible that in some patients with sickle cell anemia, who have arterial oxygen unsaturation, the pulmonary dysfunction may be of primary importance.

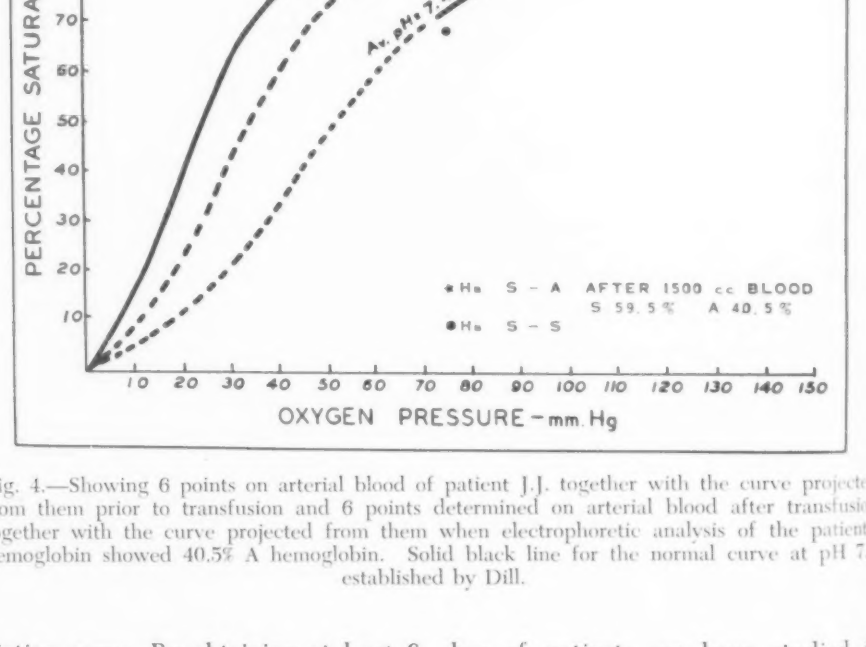


Fig. 4.—Showing 6 points on arterial blood of patient J.J. together with the curve projected from them prior to transfusion and 6 points determined on arterial blood after transfusion together with the curve projected from them when electrophoretic analysis of the patient's hemoglobin showed 40.5% A hemoglobin. Solid black line for the normal curve at pH 7.4 established by Dill.

In our patients the basic pulmonary function tests revealed little deviation

from normal except for the arterial oxygen unsaturation itself. It is unlikely that the slight reduction in vital capacity which was observed could account for the degree of arterial oxygen unsaturation unless accompanied by airway obstruction or poor alveolar mixing.

Moser and Shea[10] were impressed by the pulmonary fibrosis which complicates sickle cell anemia. They inferred a reduction in the size of the pulmonary capillary bed and suggested that a reduction in the diffusing capacity might account for the arterial unsaturation. More recently Sproule, Halden and Miller[19] have proposed increased venous admixture as the cause of the arterial unsaturation. Arterial unsaturation due to a diffusion defect can be differentiated from that due to an increased venous admixture by studying changes in the oxygen gradient between the alveolus and the arterial blood during inhalation of 2 different concentrations of oxygen (Riley, Proemmel and Franke[15]). Because of the shape of the oxygen dissociation curve a gradient which is elevated due to venous admixture will be markedly reduced on inhalation of a low concentration of oxygen. On the other hand a gradient which is elevated due to a diffusion problem will be reduced little or not at all on inhalation of a lower concentration of oxygen. Our gradient studies (Table 2) showed top normal values on ambient air which were markedly reduced on lower oxygen concentrations. This suggests that there is no diffusion problem nor increased venous admixture in our patients.

Similar or slightly larger gradients were observed by Ryan and Hickam[16] in a group of patients with anemia of various etiologies. They felt that the lower oxygen saturation of mixed venous blood frequently found in anemic patients tended to exaggerate the gradient produced by a normal venous admixture.

Rightward shift of the oxyhemoglobin dissociation curve has been reported in anemias other than sicklemia (Blumgart, Cargill and Gilligan[3], Dill *et al.*[4], Rasmussen and Storstein[12] and Richards and Strauss[14]). In the one patient whose studies were repeated following transfusion (Table 6 and Fig. 4), the curve was still markedly displaced to the right, although less so than prior to transfusion. The patient's hemoglobin was raised from 6.8 gm./100 ml. to 11.9 gm./100 ml. and electrophoretic analysis of his hemoglobin pattern at the time of the repeat studies showed 40.5% A hemoglobin and 59.5% S hemoglobin. The displacement of this patient's dissociation curve following transfusion was far greater than that which has been reported in anemia and greater than any displacement we have observed in our laboratory in anemic patients with comparable hemoglobin content. We feel, therefore, that the magnitude of the shift of the oxyhemoglobin dissociation curve that we have observed cannot be attributed to the low hemoglobin level *per se*.

The mechanism which mediates the displacement of the oxyhemoglobin dissociation curve is obscure. Wyman and Allen[22] found that dialyzed sickle hemoglobin had the same dissociation curve as normal hemoglobin similarly prepared, which suggests that the defect does not reside in the hemoglobin itself. The only factors which are known to alter the position of the oxygen dissociation curve are changes in pH and temperature. Of these, a reduced pH of the red blood cell seems the more likely to be involved. No satisfactory method of measuring the pH of the red blood cell is avail-

able at the present time so that experimental verification of this possibility must await advances in technology.

Summary. Studies in 3 patients with sickle cell anemia confirmed the presence of significant arterial oxygen unsaturation. Studies in other parameters of pulmonary function testing failed to show impairment in pulmonary function sufficient to account for this arterial oxygen unsaturation. In each patient there was a significant shift of the oxyhemoglobin dissociation curve to the right of normal, which was sufficient to explain the observed unsaturation.

REFERENCES

1. **Baldwin, E. de F., Cournand, A.,** and **Richards, D. W., Jr.:** Medicine, **27**, 243, 1948.
2. **Becklake, M. R., Griffiths, S. B., McGregor, M., Goldman, H. I.,** and **Schreve, J. P.:** J. Clin. Invest., **34**, 751, 1955.
3. **Blumgart H. L., Cargill, S. L.,** and **Gilligan, D. R.:** Ibid., **9**, 679, 1931.
4. **Dill, D. B., Block, A. V., van Caulaert, C., Fölling, A., Hurxthal, L. M.,** and **Henderson, L. J.:** J. Biol. Chem., **78**, 191, 1928.
5. **Fowler, N. O., Jr., Smith, O.,** and **Greenfield, J. C.:** Am. J. Med. Sci., **234**, 449, 1957.
6. **Fowler, N. O., Jr., Westcott, R. M.,** and **Scott, R. C.:** J. Clin. Invest., **31**, 72. 1952.
7. **Jensen, W. N., Rucknagel, D. L.,** and **Taylor, W. J.:** Ibid., **36**, 905, 1957.
8. **Kennedy, A. C.,** and **Valtis, D. J.:** Ibid., **33**, 1372, 1954.
9. **Leicht, L., Snider, T. H., Clifford, G. O.,** and **Hellems, H. K.:** Circulation, **10**, 653, 1954.
10. **Moser, K. M.,** and **Shea, J. B.:** Am. J. Med., **22**, 561, 1957.
11. **Peters, J. P.,** and **Van Slyke, D. D.:** Quantitative Clinical Chemistry, Vol. II. Baltimore: The Williams & Wilkins Co., 1932.
12. **Rasmussen, H.,** and **Storstein, O.:** Acta med. Scandinav., **141**, 52, 1951.
13. **Reinhard, E. H., Moore, C. V., Dubach, R.,** and **Wade, L. J.:** J. Clin. Invest., **23**, 682, 1954.
14. **Richards, D. W., Jr.,** and **Strauss, M. L.:** Ibid., **4**, 105, 1927.
15. **Riley, R. L., Proemmel, D. D.,** and **Franke, R. E.:** J. Biol. Chem., **161**, 621, 1945.
16. **Ryan, J. M.,** and **Hickam, J, B.:** J. Clin. Invest., **31**, 188, 1952.
17. **Scholander, P. F.:** J. Biol. Chem., **167**, 235, 1947.
18. **Scriver, J. B.,** and **Waugh, T. R.:** Canad. Med. Assn. J., **23**. 375. 1930.
19. **Sproule, B. J., Halden, E. R.,** and **Miller, F.:** J. Clin. Invest., **37**, 486, 1958.
20. **Tinsley, J. C., Jr., Moore, C. V., Dubach, R., Minnich, J.,** and **Grinstein, M.:** Ibid., **28**, 1544, 1949.
21. **Van Slyke, D. D.,** and **Sendroy, J., Jr.:** J. Biol. Chem., **79**, 781, 1928.
22. **Wyman, J., Jr.,** and **Allen, D. W.:** J. Polymer Sc., **7**, 499, 1951.

SUMMARIO IN INTERLINGUA

Le Curva Del Dissociation De Oxyhemoglobina In Anemia A Cellulas Falciforme

Studios in 3 patientes con anemia a cellulas falciforme confirmava le presentia de grados significative de non-saturation oxygenic del sanguine arterial. Tests de altere aspectos del function pulmonar non revelava defectos sufficientemente grave pro explicar le non-saturation oxygenic del sanguine arterial. Tamen, in omne le 3 patientes, le curva del dissociation de oxyhemoglobina exhibiva, in comparation con le norma, un deviation dextrorse sufficientemente significative pro explicar le observate non-saturation oxygenic.

ACUTE PLASMA CELL LEUKEMIA

By Lloyd S. Ralston, M.D.
ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF NORTH DAKOTA SCHOOL OF MEDICINE AND THE GRAND FORKS CLINIC

Walter A. Wasdahl, M.D.
FELLOW IN PATHOLOGY, UNIVERSITY OF NORTH DAKOTA SCHOOL OF MEDICINE

AND

Arthur K. Saiki, M.D.
PROFESSOR OF PATHOLOGY, UNIVERSITY OF NORTH DAKOTA SCHOOL OF MEDICINE

(From the Departments of Medicine and Pathology, University of North Dakota School of Medicine and the Grand Forks Clinic, Grand Forks, North Dakota)

Doubt has been expressed whether plasma cell leukemia exists as a clinical and pathological entity apart from multiple myeloma. It is the purpose of this paper to present a case that seems to merit the diagnosis of acute plasma cell leukemia without other findings to suggest myeloma. The course of the disease in this case was featured by high levels of circulating plasma cells and was rapidly fatal.

Case Report. This 54-year-old, obese white man had consulted his local physician in November, 1956, because of stiffness of the knees, hips, and ankles. The symptoms were of comparatively recent onset except for stiffness of the left ankle which he dated to a fracture sustained in 1925. The patient was given Butazolidin, 400 mg. daily, and placed on a weight-reduction program. The Butazolidin afforded excellent relief until July 9, 1957, at which time it was discontinued because he developed canker sores in the mouth and the leukocyte count was found to be 3,600 per c.mm.

During the week following discontinuance of Butazolidin the patient developed general malaise and was hospitalized at another hospital. He was diagnosed as having a urinary tract infection and was discharged, after antibiotic therapy, feeling better. However, following release from the hospital he again experienced general malaise, lost 30 pounds in weight, felt anorexic much of the time, and vomited once. The patient developed a severe, increasingly uncomfortable leg ache associated with a great weakness of the legs. Aside from a dull persistent frontal headache he had no other complaints. For these symptoms he was admitted to Deaconess Hospital on July 27, 1957.

Physical examination revealed an apathetic, obese white male who appeared acutely ill. The blood pressure was 140/70, pulse 110 and fully regular, temperature 99.4°, and respirations normal at a rate of 14 per minute. There was a fairly marked bilateral exophthalmos with reddened and inflamed appearing conjunctiva. The ocular fundi were normal. The chest appeared barrel shaped with increased P–A diameter, and respiratory excursions were one inch. Lungs were normal to percussion, but on auscultation moist rales were heard over both bases. The abdomen was slightly distended and was tender to palpation over the right upper quadrant. On the skin of the trunk and arms were numerous small petechiae and purpuric spots as well as many scratch marks. Excruciating tenderness was elicited by percussion or pressure on the long bones, sternum, ribs, and skull. No peripheral lymphadenopathy was found.

Laboratory. Urinalysis was negative except for 3+ albumin. Tests for Bence Jones protein were all negative. The red blood count was 2,620,000 per c.mm., the hemoglobin 9.0 gm. per 100 ml., and the hematocrit 26 vol.%. White blood cells numbered 20,500 per c.mm. with a differential count showing 2 monocytes, 16 segmented neutrophils, and 82 plasma cells. The sedimentation rate was 89 mm. per hour. Platelets were diminished on direct smear, and enumeration revealed 58,000 per c.mm. Prothrombin time

was 17 sec. (control 12 sec.). Bleeding time was 22 min., and Lee-White clotting time was 9 min. The total serum protein was 6.91 gm.% with albumin 4.8 gm.% and globulin 2.1 gm.%. Serum bilirubin direct was 0.2 mg. per 100 ml. and indirect 0.55 mg. per 100 ml., and cephalin flocculation was 2+ in 24 and 48 hours. Blood urea nitrogen was 97 mg., and creatinine was 8.45 mg. per 100 ml. Agglutinations for typhoid H and O, paratyphoid B, brucellosis, and heterophile antibody were absent. Wassermann was negative, and the electrocardiogram was within normal limits.

ROENTGENOGRAMS. Roentgen examination of the chest demonstrated multiple patchy densities in the lower left half of the left lung field giving the appearance of either slightly unusual pneumonitis or perhaps metastatic lesions. An A–P roentgenogram of the abdomen demonstrated narrowing of the intervertebral disc between L–2 and 3 with secondary sclerosis and considerable spur formation at this level. The hip joint space on the right showed narrowing with secondary cyst-like changes about the femoral head. Skull roentgenograms showed a small area of mottling in the right parietal and frontal bone. Roentgenograms of both arms and legs were normal except for evidence of an old fracture of the fibula on the left.

COURSE IN THE HOSPITAL. The patient appeared acutely ill but was oriented in all spheres. The outstanding clinical complaint was severe bone pain affecting virtually every bone in the body. Re-examination of the peripheral smear strongly suggested plasma cell leukemia. The differential white blood count on the second hospital day revealed the following: 12% segmented neutrophils, 3% nonsegmented neutrophils, 9% lymphocytes, 1% monocytes, and 75% atypical plasma cells.

The most notable aspect of the smear was the variation in morphology of plasma cells. There was greatly lessened cytoplasm in comparison to nuclei (nuclear-cytoplasmic ratio). Occasional cells appeared immature exhibiting a larger cell body, dispersed chromatin pattern, and thin cytoplasmic rim while other cells had markedly clumped chromatin. Most of the cells, whether mature or immature, had at least a hint of "flame" at the edge of the cytoplasm while the remainder of the cytoplasm was the usual deep opaque blue of the ordinary plasma cell. Throughout the smear 2 to 7 mu. cytoplasmic remnants of the abnormal cells were seen. The cytoplasm of an occasional cell appeared bubbly and moruloid.

On the second hospital day bone marrow aspiration was attempted but was unsuccessful. Bone marrow biopsy was scheduled and accomplished on July 31, 1957 (fourth hospital day). Microscopic examination of the marrow showed a markedly proliferative marrow with only a few scattered groups of fat cells remaining. Plasma cells, both mature and younger forms, largely replaced the cells of the granulocytic series. Only an occasional normoblastic or pronormoblastic area remained. The bone marrow picture was considered typical of plasma cell leukemia.

The patient's clinical condition steadily deteriorated. He became anorexic and vomited all food taken, requiring infusions of glucose and saline. Following the bone marrow biopsy he was given two units of blood on successive days (fourth and fifth hospital days) and briefly seemed improved. The morning of the sixth hospital day the patient was mildly disoriented. The pulse was 120 and fully regular, blood pressure 110/70, and temperature 99.6°. The lungs were normal to percussion but on auscultation were filled with sibilant inspiratory and expiratory rales. The liver edge was now felt 2 to 3 finger breadths below the right costal margin and was very tender to touch. Bone pain was excruciating to slightest pressure and was exhibited wherever examined. Slight ankle edema was noted. Hydrocortisone, 100 mg., was given intravenously, and because of the suggestion of congestive failure, digitalis was administered (Cedilanid, 4 ml., intramuscularly with the dosage repeated in 4 hours). At this time the CO_2 was 21 mEq./L., chlorides (serum) 515 mg. per 100 ml., serum sodium 134 mEq./L., and potassium 4.8 mEq./L. Later in the day the patient became dyspneic, and oxygen was administered by tent. He expired quietly the morning of the seventh hospital day.

Postmortem Examination: The body was that of an obese, well developed white male. External abnormalities were limited to a number of petechiae over the skin of the shoulders and back of the upper thorax. Examination of the lungs showed a diffuse, reddish-brown, mottled hemorrhagic appearance throughout both lungs, with numbers of petechiae on the pleural surfaces of the dependent portions, especially at the margins. There were numbers of diffuse and confluent hemorrhages distributed throughout both lungs. Crepitation was minimal to absent, and on pressure a considerable amount of frothy serosanguineous fluid was expressed. Examination of the abdominal cavity revealed an enlarged spleen, weighing 400 gm., with a tense capsule, that on section was composed of

firm, tan splenic parenchyma with obliterated architectural markings giving it a monotonously uniform appearance in all portions. The liver weighed 3500 gm. with rounded margins and was somewhat rubbery. On section the surface was tan, and numbers of small, up to 3 mm. in diameter, ill-defined zones of gray-white mottling were noted. This mottling appeared to be associated with the central veins. Each kidney weighed 300 gm. The capsule stripped with ease exhibiting a smooth tan cortex in which there were small, ill-defined zones of gray-white mottling. The cortex was uniform and up to 12 mm. thick, and there was noted ill-defined, grayish-white streaking at the apex of the pyramids extending peripherally. The abdominal, thoracic, and retroperitoneal lymph nodes were small, gray-white, and not remarkable. Examination of the skeletal system, including ribs, vertebrae, and skull, revealed that the bone marrow cavities were universally prominent with cortical thinning. The bone marrow was dark red and had a tendency towards fluidity. The calvarium showed a degree of thinning at the dome, but no localized tumor masses were noted in any portion of the skull on careful examination. The remainder of the skeletal system likewise revealed no tumor masses.

Microscopic: Sections of the lung showed uniform, diffuse intra-alveolar hemorrhage. In addition the alveoli contained masses of fibrin in which there were a few mononuclear cells but very little evidence of neutrophilic infiltration. The alveolar septa were thickened, and throughout all portions of the lung a diffuse infiltrate of cells with the characteristic nuclear and cytoplasmic structure of plasma cells was seen. Sections of the liver showed a uniform filling of the sinusoids with plasma cells. There was very little involvement of the portal triad, and the infiltrate was practically all sinusoidal, increasing in density towards the central veins. The spleen showed obliteration of the architecture by a diffuse infiltrate of plasma cells. An occasional macrophage filled with hemosiderin pigment was present. The kidneys revealed infiltration in the pyramids surrounding the collecting tubules. The degree of leukemic infiltration decreased as the cortex was approached, but scattered small foci were present in all areas. Numbers of the kidney

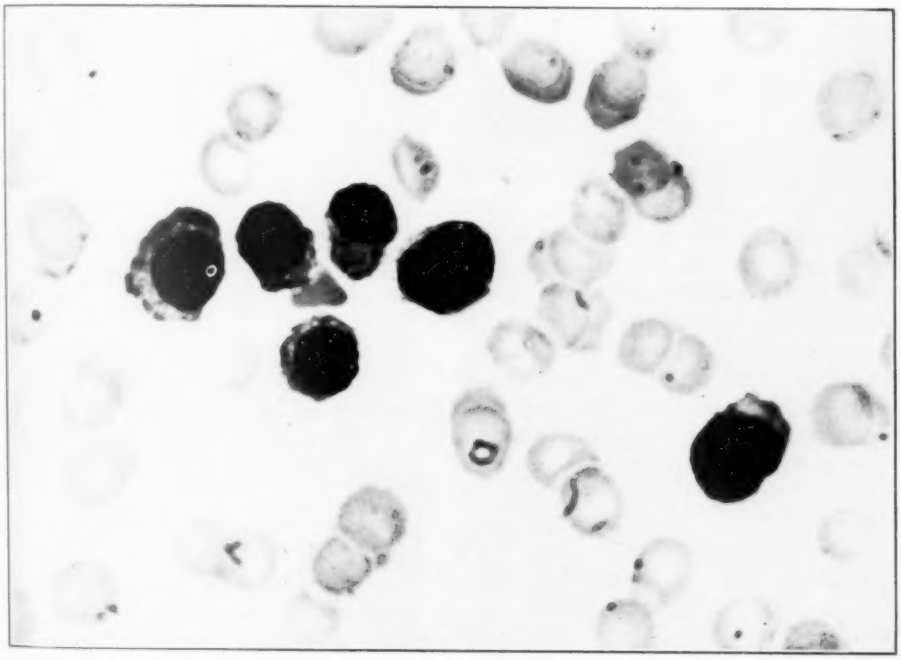


Fig. 1.—Smear of peripheral blood showing proplasmacytes and mature plasma cells.

tubules were filled with casts, some of which were large and eosinophilic, while others showed calcification. There was an occasional large multinucleated giant cell that appeared to be formed from desquamated tubular epithelium and was not associated with the casts. Smears from the bone marrow, taken at the time of necropsy, revealed replacement of bone marrow by uniform cells having the nuclear structure of plasma cells with an occasional small focus of erythropoiesis and scattered megakaryocytes. Eosinophils were present and occasional developing cells of the myeloid series were seen. Iron stains revealed considerable hemosiderosis throughout the bone marrow. The picture was that of a diffuse replacement by plasma cells without localized aggregates. Sections of lymph nodes showed the architecture to be preserved with a mild increase in plasma cells within the sinusoids; however, no apparent parenchymal replacement was seen.

Discussion. This patient had a rapidly downhill course, actually 7 days from the time of diagnosis to death. Whether his complaint of arthritic-like pain 9 months previously actually represented the onset of his illness cannot be stated. It will be recalled, however, that degenerative arthritic changes were seen in the lumbar spine and the right hip plus changes in the left leg incident to the ancient fracture as a possible explanation for these early symptoms. To our knowledge Butazolidin has never been linked to a proliferative phenomenon, and any possible connection in this case would seem purely conjecture. Unfortunately a differential count was not obtained on July 9, 1957, when the drug was stopped because of depression of the white blood count to 3,600 per c.mm. Whether this represented an "aleukemic" phase of the plasma cell process cannot be stated.

The acute symptoms (general malaise, rapid weight loss, and bone pain) are those usually recorded in acute plasma cell leukemia.

Bence Jones proteinuria was not demonstrated on repeated careful testing. Elevation of the white blood count persisted throughout the brief course with plasma cells numbering up to 82% of the peripheral circulating white blood cells. The total protein, serum albumin and globulin values were all within the normal range. Virtually complete bone survey by roentgenography revealed no localized tumor mass. At necropsy gross and microscopic examination showed massive plasma cell infiltration of the lung, liver, spleen, kidney, and bone marrow with an associated lesser involvement of lymph nodes. No discrete tumor masses were found in bone. This case would then seem to merit the diagnosis of acute plasma cell leukemia.

Askanazy and Dubois-Ferriere[1] have suggested the following criteria be fulfilled in establishing the diagnosis of plasma cell leukemia.

1. Plasma cells must be present in the peripheral blood during the entire course of the disease.
2. Leukocytosis should be exhibited.
3. Widespread bone marrow involvement with plasma cells should be present.

Moss and Ackerman[8] point out that this list does not consider a possible aleukemic phase. The latter authors suggest the only necessary criteria to be a bone marrow biopsy exhibiting diffuse plasma cell infiltration associated with typical plasma cells in the peripheral blood. Clinical signs and symptoms of leukemia are regarded as helpful but not necessarily present.

It should be noted that other conditions may be associated with either circulating plasma cells or increased plasma cells in bone marrow. In the peripheral blood, plasma cells numbering up to 30% have been reported in association with measles (Naegeli[9]), rubella, rubeola, scarlatina (Cronk[2]), chronic lymphatic leukemia (Pappenheim[12]), myeloid leukemia, metastatic

carcinoma in bone, Hodgkin's disease (Patek and Castle[13]), gonorrhea (Piney[14]), and infectious mononucleosis (Meyer, Halpern, and Ogden[6]) If diligently sought, these cells are said to be not uncommonly found in the peripheral blood of multiple myeloma patients (Meyer and Rutzky[7]).

Plasma cell infiltration of bone marrow in the absence of any appreciable number in the peripheral blood has been reported. Moss and Ackerman[8] note this finding in hepatic cirrhosis, agranulocytosis, miliary tuberculosis, and in some hypoplastic anemias. Other conditions which may exhibit plasmacytosis of marrow are lupus erythematosus, Boeck's sarcoid, kala azar, lymphopathia venereum (Snapper, Turner, and Moskovitz[16]), Hodgkin's sarcoma, lymphosarcoma, acute monocytic leukemia, primary "refractory" anemia, hiatal hernia, and papilloma of bladder (Fadem and McBirnie[3]). In general this should cause little diagnostic confusion.

A relationship between plasma cell leukemia and multiple myeloma has been considered by many workers (Patek and Castle[13], Osgood and Hunter[11], and Jackson, Parker, and Bethea[5]). Piney and Keck[15] have collected cases representing stages from typical myeloma to typical plasma cell leukemia. This is somewhat reminiscent perhaps of the relationship between lymphosarcoma and lymphatic leukemia and might be used in further support of the concept of unity in plasma cellular neoplasia (Newman *et al.*[10]). It has been suggested by Patek and Castle[13] that the closer the resemblance of plasma cell leukemia to typical leukemia the more malignant the process tended to become. This is borne out in the presently reported case. Further substance is gained by comparison of life span in the average case after recognition of symptoms. In multiple myeloma the average is reported as 2 years (Geschickter and Copeland[4]) while in plasma cell leukemia it is 8 months (Moss and Ackerman[8]).

The presently reported case fulfills all the criteria necessary for a diagnosis of acute plasma cell leukemia. When one considers other leukocytic tumors and leukemias (lymphosarcoma and lymphatic leukemia; chloroma and myelogenous leukemia; as well as plasmacytoma, multiple myeloma, and plasma cell leukemia) it seems somewhat difficult to regard this as a disease entity distinct from multiple myeloma. Regardless of the obvious relationship to multiple myeloma, the term plasma cell leukemia would seem to have utility for clinical, prognostic, and possibly therapeutic reasons.

Summary. A case of plasma cell leukemia is described. The course of the disease was rapidly fatal with no features to suggest multiple myeloma.

Brief consideration is given to diagnostic criteria as well as other diseases presenting plasmacytosis of peripheral blood or bone marrow.

The close relationship of plasma cell leukemia to multiple myeloma is noted.

REFERENCES

1. Askanazy, M., and **Dubois-Ferriere, H.:** Helvet med. Acta, **9**, 427, 1942.
2. Craik, R.: Brit. Med. J., **2**, 1096, 1923.
3. Fadem, R. S., and **McBirnie, J. E.:** Blood, **5**, 191, 1950.
4. Geschickter, C. F., and **Copeland, M. M.:** Arch. Surg., **16**, 807, 1928.
5. Jackson, H., Jr., **Parker, F., Jr.,** and **Bethea, J. M.:** Am. J. Med. Sci., **181**, 169, 1931.
6. Meyer, L. M., **Halpern, J.,** and **Ogden, F. N.:** Ann. Int. Med., **22**, 585, 1945.

7. **Meyer, L. M.,** and **Rutzky, J.:** Cancer, **4**, 1043, 1951.
8. **Moss, W. T.,** and **Ackerman, L. V.:** Blood, **1**, 396, 1946.
9. **Naegeli, O.:** Blutenkrankheiten und Blutdiagnostik; Lehrbuch der Klinischen Hematologie, Fourth Ed. Berlin: Julius Springer, 1923.
10. **Newman, W., Diefenbach, W. C. L., Quinn, M.,** and **Meyer, L. M.:** Cancer, **5**, 514, 1952.
11. **Osgood, E. E.,** and **Hunter, W. C.:** Folia Haemat., **52**, 369, 1934.
12. **Pappenheim, A.:** Morphologische Hematologie. **Hirshfeld, H.,** Ed. Leipzig: Werner Kluikhardt, **2**, 188, 1919.
13. **Patek, A. J.,** and **Castle, W. B.:** Am. J. Med. Sci., **191**, 788, 1936.
14. **Piney, A.:** Folia Haemat., **30**, 174, 1924.
15. **Piney, E. D.,** and **Keck, F. J.:** Arch. Surg., **16**, 807, 1928.
16. **Snapper, I., Turner, L.,** and **Moskovitz, H.:** Multiple Myeloma. New York: Grune & Stratton, Inc., 1953.

SUMMARIO IN INTERLINGUA

Acute Leucemia A Cellulas Plasmatic

Es describite un caso de leucemia a cellulas plasmatic. Le curso del morbo es rapidemente mortal. Nihil in illo suggereva myeloma multiple.

Es considerate brevemente le criterios diagnostic e etiam altere morbos que exhibi plasmocytosis del sanguine peripheric o del medulla ossee.

Es notate le intimitate del relation inter leucemia a cellulas plasmatic e myeloma multiple.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

I. S. RAVDIN, B.S., M.D.
JOHN RHEA BARTON PROFESSOR OF SURGERY, UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PENNSYLVANIA

AND

C. G. JOHNSTON, M.S., M.D.
PROFESSOR OF SURGERY, WAYNE UNIVERSITY
DETROIT, MICHIGAN

THE SURGICAL TREATMENT OF PORTAL HYPERTENSION

BY T. B. PATTON, M.D.
ASSOCIATE PROFESSOR OF SURGERY, MEDICAL COLLEGE OF ALABAMA

AND

C. G. JOHNSTON, M.S., M.D.

(From the Departments of Surgery of the Medical College of Alabama, Birmingham, Alabama, and Wayne State University College of Medicine, Detroit, Michigan)

WHEN portal flow is impeded, portal hypertension is one of the sequelae. The most striking clinical consequence of this is massive upper gastrointestinal hemorrhage from esophageal or gastric varices. Less frequently there may be massive melena, and at times ascites is the presenting complaint. Many methods have been devised to prevent exsanguination during these episodic bleeding crises. It is now generally recognized that the untoward metabolic complications of hemorrhage into the gastrointestinal tract are as important as the loss of blood. It is the purpose of this review to discuss the prevention and treatment of the hemorrhagic complications of portal hypertension.

Bleeding Varices. ETIOLOGY. The dilated esophageal varix is but a reflection of increased tension in the portal system. In 1900, Preble[109] documented 60 cases of hematemesis with esophageal varices indicted as the cause. The precise mechanism for increase in portal pressure is unknown[9]. It has been shown that during physiologic acts, producing a Valsalva response, the pressure in the portal system exceeds critical levels at which bleeding from varices occurs[127]. Whipple[137], in 1945, classified portal hypertension into two categories: intra- and extrahepatic

portal bed block. Various theories have been postulated to account for intrahepatic block. The fibrosis which accompanies cirrhosis is thought to compress the portal venous radicles. McIndoe[85] believed that hepatic venules were compressed, and Kelty[60] believed that regeneration of liver parenchyma caused pressure on all intrahepatic veins. Most recently five separate sets of mechanisms have been described which can control passage of blood from the portal bed and the liver: (1) contractile hepatic veins; (2) contractile sublobular veins; (3) Deysach small sluice channel; (4) sinusoid outlet sphincters; (5) smooth muscle fibers arching around the outlet orifices of the large hepatic veins[64]. Portal hypertension, most frequently associated with Laennec's cirrhosis, has also been reported in postnecrotic cirrhosis[97,123,141], schistosomiasis[95], Boeck's sarcoid[38], hemochromatosis[62], syphilis[67], Cruveilhier-Baumgarten syndrome[51], pericarditis[88], and scleroderma[24].

Extrahepatic portal bed block is caused by thombosis in the portal vein itself or in some portion of the portal collecting system. The precise mechanism for the thrombosis is not clearly delineated. It may occur *in utero* and may be the result of extension of umbilical vein thrombosis at the time of birth[49]. Other theories presented are congenital anomalies, or angioma of the portal vein[63], or inferior vena cava[6,50,55,59,86,94]. Thrombosis of the portal vein has been observed following blunt or penetrating abdominal trauma, pylephlebitis, splenectomy, and as a complication of polycythemia vera[19]. Infrequently, one can obtain a history of umbilical infection in the first week of life. Tumors and inflammation, often of pancreatic or lymph node origin, may cause extraluminal compression of this structure[138]. Arteriovenous fistula between the hepatic artery and portal vein has been reported[78]. Be that as it may, if the portal vein is thrombosed, a thin-walled dilated plexus of veins results from an effort to by-pass this obstructed venous segment. This condition is commonly, if erroneously, designated as cavernous transformation of the portal vein. It is usually seen in infants and young children without intrinsic liver disease, and, under these circumstances, may well represent an angiomatous anomaly.

DIAGNOSIS. When massive hematemesis occurs, accurate identification of its origin is mandatory. Gastric ulcer, duodenal ulcer, alcoholic gastritis, superficial gastric erosions, are frequently associated in the cirrhotic patient.

A rapid physical examination will reveal the stigmata of cirrhosis, including spider angiomata[18,21], liver palms, sparse pubic, axillary and facial hair. Gynecomastia and testicular atrophy may be seen in males. In children the only clue may be an enlarged spleen[55]. The so-called caput Medusae is an infrequent finding. Hemorrhoids may be present.

There are three laboratory tests which have been of value consistently. The prothrombin time is depressed in cirrhotic patients usually below 50% while it is minimally altered in patients bleeding from duodenal ulcer[15]. The Bromsulphalein test is markedly abnormal in patients with intrinsic liver disease and unaffected in patients bleeding from another cause[140]. The blood ammonia level is elevated in patients with liver disease and is normal in patients with bleeding duodenal ulcer[75].

In our experience, these patients have been too ill to tolerate esophagoscopy and results of this procedure have been hard to evaluate. The varices may

be collapsed because of the bleeding episode, and the constant welling-up of blood in the scope from the stomach or esophagus makes precise identification of the bleeding area exceedingly tedious. During the active bleeding phase roentgenograms are difficult to interpret because of prior collapse of the veins or presence of confusing clots.

Emergency Treatment. A. NONOPERATIVE. If a patient presents himself with massive hematemesis, two problems immediately confront a surgeon. The most urgent is control of hemorrhage and restoration of the depleted blood volume. The other is precise identification of the source of bleeding. Whole blood, freshly drawn in plastic bags to preserve the clotting factors, should be given. Old, banked blood has an increased ammonia content and diminished platelet and prothrombin content[28]. Pneumatic tamponade of the lower esophagus should be employed initially. This is no new concept, since it was suggested by French physicians late in the 19th century[109]. Tamponade was first employed by Westphal[136] and through the years, with technologic advances, modifications of this concept have been presented[10,57,91,99,115,119,128]. Bleeding from esophageal varices occurs from those veins in the terminal 4 to 5 cm. of the esophagus and proximal portion of the stomach. Frequently there are erosions of the mucosa at the esophagogastric junction. Examination of postmortem specimens and direct observations of bleeding sites during emergency ligations of bleeding varices confirm this fact. Tamponade not only compresses the bleeding area and controls hemorrhage but provides an accurate differential diagnosis of the site of bleeding[27,75]. There are several pitfalls in the use of tamponade aside from technical difficulties such as displacement and lack of adequate inflation[58]. When gastric varices occur, as they do in 2% of these patients[117,121], tamponade is not effective. It is, therefore, necessary to evaluate these patients every 4 hours[100]. If there has been no bleeding after 4 hours of continuous tamponade, the upper balloon is deflated, the lower balloon is left inflated so that the tube may be in position if blood appears in the gastric aspirate after the release of pressure in the upper balloon. If no bleeding has occurred in 8 hours, the lower balloon is deflated and the tube is used for transport of saline cathartics to evacuate blood rapidly from the gastrointestinal tract[134]. If bleeding has not recurred in 24 hours, the tube is removed and these patients are started on a progressive diet. If the gastric aspirate continues to be bloody during the first 24-hours of tamponade, operative intervention must be considered. A slavish reliance on tamponade while bright red blood continues in the gastric aspirate may spell disaster, because the original diagnosis may be in error. Gastric varices may be the source of bleeding and the association of duodenal ulcer (20% in the cirrhotic patient) is a matter of record[42,96]. Tamponade continued for more than 24 hours will cause inflammatory edema and superficial erosions of the esophagus[23]. Both of these complications jeopardize healing of the esophagus, if surgical intervention becomes necessary. Prolonged bleeding is especially detrimental to these depleted patients and hemorrhage continuing for more than 24 hours is an indication for surgical intervention unless the patient is a dead-end cirrhotic. In this latter instance, long-continued tamponade (continued in one of our cases for 7 days) seems preferable.

Other nonoperative procedures, used in the past and now abandoned, were the application of tannic acid locally[57] and the injection of the varices with sclerosing solutions[33,87].

B. OPERATIVE. Emergency operations

fall into two categories. One is an attack on the bleeding varix; the other, the performance of a shunt to lower the portal pressure and control bleeding varices indirectly. Splenectomy[3,31,81,107], ligation of coronary veins[115], arterial ligations[2,7,8,11,12,41,76,77,84,112,124], mediastinal tamponade, and esophagogastrectomy[108] have been tried over the last 40 years but none has proven satisfactory.

Currently there are two surgical approaches to control the bleeding varix: the transthoracic[17,34,69] and the transabdominal[32,135]. The transabdominal approach is better tolerated by the patients and does not limit mobilization of the esophagus. It has the further advantage of permitting a direct approach to complicating or previously unrecognized gastric varices or gastric or duodenal ulcer. The transthoracic approach is reserved for those patients with previous left upper quadrant incisions. Only the varices in the last 4 to 5 cm. of the esophagus need be oversewn, but the suture line should include a portion of the adjacent gastric mucosa.

Emergency shunt procedures, maintaining tamponade until portal diversion is accomplished, have not gained wide acceptance although they are performed more generally and more successfully in the better risk patient[25,70].

ELECTIVE TREATMENT. If there is adequate hepatocellular function, definitive treatment of portal hypertension is generally considered[16,93] to be construction of shunts between the portal and caval systems.

In 1877 Eck accomplished complete portal diversion in the dog by performing a lateral anastomosis between the portal vein and the inferior vena cava and ligated the portal vein above the shunt. He suggested that this procedure might be of benefit in the treatment of cirrhotic patients with ascites[26].

Tansini[126], in 1902, was the first to perform anastomosis of the distal end of the portal vein to the side of the inferior vena cava. This procedure is generally called the Eck fistula today.

The first successful shunt was performed by Vidal in 1902[129]. From his comments made in 1910[130], it is evident that he was aware that portal hypertension caused hematemesis in the cirrhotic patient. He performed a fistula instead of an omentopexy to control esophageal hemorrhage. Even at this early time there was marked disagreement regarding the type shunt to be performed. Franke[44] and Jerusalem[53] challenged the wisdom of complete portal diversion and advocated the lateral portacaval anastomosis which permitted portal bed decompression and an increment of portal blood to flow on to the liver. The first successful lateral portacaval anastomosis was performed by Rosenstein in 1912[113].

Because of the high mortality, shunt procedures were not widely practiced for 30 years. Many other elective surgical procedures were devised to control the effects of portal hypertension. None of these procedures has been eminently successful. Splenectomy has been used in the treatment of portal hypertension for almost 100 years. It has not proven effective because existing collaterals are abrogated, and the dilated portal bed is still further contracted by removal of this reservoir[54]. Moreover, removal of the spleen may nullify the only chance for the performance of a shunt between the portal circulation and the general venous circulation especially in those patients who have portal thrombosis or cavernous transformation of the portal vein[71].

Visceral extirpation was carried out primarily to remove the varix-bearing area and diminish the amount of blood flowing into the portal system. These procedures and their various modifica-

tions, that is, total gastrectomy, esophagogastrectomy, esophagojejunostomy, associated with splenectomy or vagotomy, have failed[4,5,46,106,108,120,131,139]. Such operations have not imposed a barrier between the submucosal esophageal plexus of veins and the portal system. Indeed, acid peptic reflux is not the sole cause of initiation of bleeding from the dilated plexus of esophageal veins. Procedures of this magnitude are poorly tolerated by the patient with hepatic disease, and no reduction in portal pressure results from surgically contracting the portal bed[101].

Rienhoff[112] and Berman[7,8] sought a solution to this problem by ligation of the hepatic, splenic, and left gastric arteries. By diminishing hepatic arterial flow to the liver congestion in the liver was reduced, and it was thought a cessation of bleeding and ascites would occur because of this diminution in portal pressure. The generally poor results[2,76,77] with this technique suggest that portal hypertension is not significantly dependent upon hepatic arterial shunts to the portal system.

In 1945 Whipple[137], Blakemore, and Lord[13,14] revived interest in the portacaval shunt by their advocacy of the procedure. It was demonstrated that this procedure would effectively lower elevated levels of pressure in the portal system. Initially, they employed a nonsuture technique[14]. The proximal end of the portal vein was ligated near the hilum of the liver and the distal end of the portal vein passed through a Vitallium prosthesis and cuffed back over this tube. The end of the portal vein was placed in an incision in the inferior vena cava and held there by a purse-string suture. Thrombosis occurred all too frequently with this method, and it was abandoned for the direct suture technique devised by Blakemore[15]. This suture is an everting intima-to-intima anastomosis. This is most important; for by using this technique, thrombosis is markedly reduced. This is apparent, not only in our laboratory animals whose lateral portacaval anastomoses have remained patent for 3 years[102], but also in our series of patients in which lateral portacaval shunts have been found closed in only 2 of 11 postmortem examinations[103].

Whipple, Blakemore, and Lord used portacaval and splenorenal shunts, sacrificing the left kidney for the splenorenal procedure. Linton was first to point out that the kidney need not be sacrificed and effected an end to side anastomosis of the splenic vein to the renal vein[72].

In 1948 we began to perform shunts and, with few exceptions, have preferred the lateral portacaval type anastomosis. We routinely have used a right subcostal incision with the right side of the patient elevated so that the approach to the portal vein may be more direct. The combined thoracoabdominal incision was used in several cases, and the only complaint these patients have, 8 to 10 years later, is that their ribs remain sore and tender. When there is caudate lobe hypertrophy which will not permit approximation of the portal vein and inferior vena cava without undue tension or angulation, we have used a vein graft to bridge these structures[110].

A real contribution was made in 1951 when Abeatici and Campi[1] showed that the portal system could be outlined precisely by injection of dye into the spleen. This procedure rapidly identifies the ideal site for performance of a shunt and saves much tedious dissection and blood loss. One can tell in a few minutes whether or not the portal vein is patent and suitable for a shunt. There is a risk of hemorrhage with the use of percutaneous splenic puncture[36,98,111], and we have performed

splenoportagrams and portaportagrams under direct vision at the time of laparotomy. The dye is injected through the same polythene tube, previously placed, used for the measurement of portal tension. Normal portal pressure is conceded to be between 80 to 180 mm. of saline solution, and pressures of 300 mm. of saline or more constitute a definite indication for a shunt procedure[22].

Mortality rates for the shunt procedure range from 6 to 20%, if all patients are included. The mortality rate for patients with extrahepatic obstruction is significantly lower, 0 to 3%, and there has been no mortality in our series of cases[103]. Including all patients who have had a lateral portacaval anastomosis, our own mortality figures are 16.9%[103].

Problems to be Solved. Many brilliant contributions have been made in the past 50 years to the treatment of portal hypertension, but many of the same problems confronting us today were the subject of debate at the turn of the 20th century.

(1) THE TYPE SHUNT TO BE EMPLOYED. Shunts, as performed today, are of three types: Eck, splenorenal, and lateral (side to side) portacaval anastomosis. Of these, the Eck and splenorenal shunt have gained widest acceptance, since only Longmire and the authors have employed the side-to-side anastomosis consistently.

Those favoring the Eck fistula type anastomosis believe that more adequate decompression of the portal system is possible. They also postulate that no portal blood reaches the liver because of the extensive fibrosis in this organ. Further, it is stated that the lateral portacaval anastomosis may actually provoke a reverse flow of blood and decrease the amount of blood available to the damaged liver. Recently Longmire[74] has shown that a reversal of flow is a mechanism seen in normal livers during the resting phase. These studies were carried out using radioactive iodinated albumin. During the absorptive phase in dogs with lateral portacaval anastomosis, there was no reversal of flow. The criticism is also leveled that the side-to-side anastomosis clots more readily, but this is not substantiated in our animal experiments or clinical experience. The necessity for excising an ellipse of vein wall on both the portal vein and the inferior vena cava has been repeatedly emphasized and the everting intima-to-intima suture must be employed[66].

The splenorenal shunt was favored because it was originally thought that hypersplenism demanded removal of the spleen, and it was hoped that a certain amount of blood would reach the liver and prevent intolerance to dietary protein. Indeed it was stated that there was relative infrequency of ammonia intoxication following the performance of this type of shunt[73]. It has become apparent that the spleen need not and should not be removed[25, 51]. By so doing, existing spontaneously formed collaterals are destroyed, and the reservoir function of the spleen abolished. The procedure is technically difficult, tedious, and to obtain an adequate length of splenic vein, a vein graft is often necessary[114]. When venous grafts are necessary in this type of shunt, they have a tendency to close when the pressure in the portal system is lowered[56]. This type of shunt should be reserved for those patients having thrombosis or cavernous transformation of the portal vein.

Proponents of the lateral anastomosis prefer it because not all of the portal blood is diverted from the liver. Mann, in his series of experiments, proved that without portal flow there was no regeneration of liver parenchyma[79]. It would also appear from a perusal

of the literature that there is a greater incidence of hepatic coma following the Eck fistula anastomosis[27,39,48,51,52,82,132] than with the lateral portacaval anastomosis[66,68]. Indeed, hepatic coma occurred following complete portal diversion where no intrinsic liver disease was present[83]. In our experimental studies, complete portal diversion plus liver damage with the added insult of high levels of circulating ammonia was incompatible with survival[104]. In our series of 67 lateral portacaval anastomoses, we have had 2 deaths from hepatic coma in the immediate postoperative period, and none on long-term follow-up. Transient episodes of pre-coma with elevated ammonia levels have been seen and treated in 2 other patients[100].

(2) HEPATIC COMA. As previously stated, there would appear to be a greater incidence of hepatic coma following the Eck fistula anastomosis than is seen with the lateral portacaval anastomosis. In our series patients usually get into difficulty during holidays or feast days when dietary protein[80] is markedly increased. In these patients blood ammonia levels have been elevated but have responded to a regimen of restriction of dietary protein and the use of arginine hydrochloride[92] and monosodium glutamate[133]. If bleeding has occurred, the addition of neomycin[43] following a saline purge to diminish bacteria in the gut has been helpful[134]. This is a thorny road, for all of the signs and symptoms of hepatic coma have been reported in patients with no evidence of liver disease and without demonstrable elevations of the blood ammonia levels[122].

(3) INFANTS AND YOUNG CHILDREN. Hematemesis seen in infants and young children is usually due to extrahepatic portal bed block[20,26,55]. The small size of the vessels makes the fashioning of a functioning shunt difficult and there is a high incidence of closure. Our poorest results have been in this group, for rebleeding episodes occur with alarming frequency[61,120]. We have abandoned attempts to perform shunts in these children unless a fortuitously large vein is found and have placed increasing reliance on transesophageal ligation as a temporary expedient. We are now attempting to carry these children to the age of 10 years when a definitive shunt will be attempted with some assurance of patency due to increase in size of the vessels. Koop[65] has advocated substitution of the colon for the lower end of the varix-bearing area in the esophagus, but this procedure needs a longer period of evaluation.

(4) PEPTIC ULCER. Mulligan[90] and Longmire have been impressed with the occurrence of peptic ulceration as a complication of portal hypertension. In Mulligan's series 8 of 45 patients developed gastric ulcer after the performance of an end-to-side shunt. Longmire's group[29] has postulated faulty hepatic inactivation of a gastric secretogogue in consequence of diversion of blood from the hepatic circulation to the systemic venous flow. This diversion may result from spontaneous collaterals, and is, of course, increased by a surgical shunt. We are currently evaluating this concept by fashioning Pavlov pouches in dogs. At such times as these pouches function we are performing Eck fistulas and side-to-side anastomoses so these animals may be contrasted with a control series[105]. It will be important to define this secretogogue more precisely and attempt to define its dietary precursors.

(5) BLEEDING EPISODES FOLLOWING PREVIOUS OPERATIVE MEASURES. There is a group of patients who re-bleed after any type procedure has been performed, including shunts. We be-

lieve that all of these patients should be re-explored and that the portal system should be outlined by the use of portagrams. If enlarged, dilated collaterals are present, it may be possible to construct some type of anastomosis between the portal system and the general venous circulation[30,47,100]. There is no question that these shunts are definitely inferior to the portacaval type of anastomosis but may provide a long period of improvement. Two of our patients in whom this was done, have not bled for 3 years and 18 months respectively[101].

(6) ASCITES. Ascites[40] is usually a complication in dead-end cirrhotics whose liver function is too poor to stand a long procedure. An adequate trial of medical management and, lately, the use of chlorthiazide[89], have been productive of the best results. Paracentesis should be deferred and should be used only when respiratory embarrassment is evident.

It is of interest that the first portacaval shunts were performed for ascites. In 1896 Drummond and Morison[37] and in 1898 Talma[125] proposed omentopexy for the treatment of ascites. The omentum was sutured to the abdominal wall to create vascular adhesions. It was postulated that the portasystemic shunts so formed would relieve the ascites. This procedure was generally unsuccessful. Numerous procedures were devised to drain ascitic fluid directly into the venous system by anastomosing the peritoneal cavity to the proximal end of the saphenous vein. This was not effective. More recently, the Crosby-Cooney button[35] was also devised for relief of ascites. This, too, was unsuccessful. Rienhoff[112] and Berman[7,8] advocated ligation of the hepatic splenic and left gastric artery and reported some success in patients with ascites. Results of this procedure are not consistently reproduced.

Ligation of one of the hepatic ducts as a means of providing a stimulus for regeneration of the remaining unobstructed portion of the liver has been tried and good results reported in one patient[118]. The obstructed portion of the liver becomes atrophic, but there is regeneration of liver tissue in the unobstructed portion. Our only trial of this procedure resulted in the death of the patient in coma 7 days postoperatively.

Unfortunately there is no procedure currently practiced which offers definite benefit in ascites. We have noticed postoperative ascites more frequently in patients with postnecrotic cirrhosis following the performance of a shunt. This improves slowly on medical management.

Child has recently recommended portal decompression in patients with ascites who have adequate liver function after a long trial of medical management has been carried out without benefit[25].

We hope that by reviewing previous concepts of therapy, we can evaluate present-day treatment, avoid compounding errors of previous work in this field, and deal adequately with the problems that remain.

ACKNOWLEDGMENT: The authors wish to thank Dr. Champ Lyons for his criticism and help in the preparation of this paper.

REFERENCES

(1) **Abeatici, C.,** and **Campi, L.:** Minerva Med., **42,** 593, 1951. (2) **Altemeier, W. A., McElhinney, W. T.,** and **MacMillan, B. G.:** A.M.A. Arch. Surg., **71,** 571, 1955. (3) **Andrus, W. DeW.,** and **Holman, C. W.:** Ann. Surg., **109,** 64, 1939.

(4) **Barnes, W. A.,** and **Redo, S. F.:** Ibid., **146,** 224, 1957. (5) **Baronofsky, I. D.:** Surgery, **25,** 135, 1949. (6) **Bennett, I. L., Jr.:** Bull. Johns Hopkins Hosp., **87,** 290, 1950. (7) **Berman, J. K., Koenig, H.,** and **Muller, L. B.:** A.M.A. Arch. Surg., **63,** 379, 1951. (8) **Berman, J. K.,** and **Hull, J. E.:** Ibid., **65,** 37, 1952. (9) **Berman, J. K.:** Ibid., **71,** 596, 1955. (10) **Bixby, E. W., Jr.:** J. Am. Med. Assn., **138,** 908, 1948. (11) **Blain, A. W.:** Surg., Gynec. & Obst., **26,** 660, 1918. ((12) **Blain, A. W.,** and **Blain, A. III:** Ann. Surg., **131,** 92, 1950. (13) **Blakemore, A. H.,** and **Lord, J. W., Jr.:** Ibid., **121,** 435, 1945. (14) Iidem: Ibid., **122,** 476, 1945. (15) **Blalock, A.:** Ibid., **125,** 129, 1947. (16) **Blond, K.:** J. Internat. Coll. Surg., **27,** 528, 1957. (17) **Boerema, I.:** Nederl. tijdschr. v. geneesk., **93,** 4174, 1949. (18) **Bouchard:** Rev. de Med., **2,** 295, 1902. (19) **Brandenburg, R.:** Acta path. et microbiol. Scandinav., **3,** 521, 1926. (20) **Brayton, D.,** and **Norris, W. J.:** J. Am. Med. Assn., **156,** 31, 1957. (21) **Brick, I. B.,** and **Palmer, E. D.:** Ibid., **155,** 8, 1954. (22) **Browne, D. C.,** and **Welch, G. E.:** Ibid., **158,** 106, 1955. (23) **Buford, T.:** Personal communication.

(24) **Calvert, R. J., Barling, B., Sopher, M.,** and **Feiwel, M.:** Brit. Med. J., **1,** 22, 1958. (25) **Child, C. G. III,** and **Donovan, A. J.:** Am. J. Digest. Dis., **3,** 114, 1958. (26) **Child, C. G. III:** Surg., Gynec. & Obst., **96,** 375, 1953. (27) Idem: Hepatic Circulation and Portal Hypertension. Philadelphia: W. B. Saunders Co., 1954. (28) **Cincotti, J. J.:** Ann. Surg., **142,** 566, 1955. (29) **Clark, J. S., Ozeran, R. S., Hart, J. C., Cruze, K.,** and **Crevling, V.:** Meeting Am. Surg. Assn., April, 1958. (30) **Clatworthy, H. W., Jr., Wall, T.,** and **Watman, R. N.:** A.M.A. Arch. Surg., **71,** 588, 1955. (31) **Cole, W. H., Majarakis, J. D.,** and **Limarzi, L. R.:** Ibid., **71,** 33, 1955. (32) **Cole, W. H.:** Personal communication. (33) **Crafoord, C.,** and **Frenckner, P.:** Acta oto-laryng., **27,** 422, 1950. (34) **Crile, G., Jr.:** A.M.A. Arch. Surg., **61,** 654, 1950. (35) **Crosby, R. C.,** and **Cooney, E. A.:** New England J. Med., **235,** 581, 1946.

(36) **Davis, C. G., Jr.:** A.M.A. Arch. Surg., **72,** 887, 1956. (37) **Drummond, D.,** and **Morison, R.:** Brit. Med. J., **2,** 278, 1896. (38) **Dunlap, R. W., Sr., Hollenbeck, G. A.,** and **Hanon, D. G.:** Proc. Staff Meet., Mayo Clin., **27,** 266, 1952.

(39) **Ebeling, W. C., Bunker, J. P., Ellis, D. S., French, A. B., Linton, R. R.,** and **Jones. C. M.:** New England J. Med., **254,** 141, 1956. (40) **Erasistratus:** 304 B.C., cited by **Rolleston, H. D.:** Diseases of Liver, Gall Bladder, and Bile Ducts. New York: Macmillan and Co., Ltd., 1912. (41) **Everson, T. C.,** and **Cole, W. H.:** A.M.A. Arch. Surg., **56,** 153, 1948.

(42) **Fainer, D. C.,** and **Halstead, J. A.:** J. Am. Med. Assn., **157,** 413, 1955. (43) **Fisher, C. J.,** and **Faloon, W. W.:** New England J. Med., **255,** 589, 1956. (44) **Franke, E.:** Verhandl. deutsch. Gesellsch. f. Chir., **40,** 267, 1911. (45) **Frommeyer, W. B., and Epstein, R. D.:** New England J. Med., **241,** 700 and 743, 1949.

(46) **Gray, H. D.,** and **Whitsell, F. B.:** Ann. Surg., **132,** 798, 1950.

(47) **Hallenbeck, G. A.,** and **Shocket, E.:** A.M.A. Arch. Surg., **71,** 581, 1955. (48) **Havens, L. L.,** and **Child, C. G. III:** New England J. Med., **252,** 756, 1955. (46) **Hollenburg, H. C.,** and **Briggs, B. P.:** Ann. Surg., **141,** 648, 1955. (50) **Huseby, R. A.,** and **Boyden, E. A.:** Anat. Rec., **81,** 537, 1941.

(51) **Jahnke, E. J., Jr., Palmer, E. D.,** and **Brick, I. B.:** Ann. Surg., **140,** 44, 1954. (52) Iidem: Surg., Gynec. & Obst., **97,** 471, 1953. (53) **Jerusalem, E.:** Verhandl. deutsch. Gesellsch. f. Chir., **42,** 271, 1911. (54) **Johnston, C. G.:** Personal communication. (55) **Jordan, P., Jr., Patton, T. B.,** and **Benson, C. G.:** A.M.A. Arch. Surg., **72,** 879, 1956. (56) **Julian, O. C.:** Surg., Gynec. & Obst., **100,** 753, 1955.

(57) **Kaplan, B.:** Med. Rec., **154,** 176, 1941. (58) **Kark, R.:** J. Am. Med. Assn., **158,** 120, 1955. (59) **Keen, J. A.:** Brit. J. Surg., **29,** 105, 1941. (60) **Kelty, R. H., Baggenstoss, A. H.,** and **Butt, R.:** Gastroenterology, **15,** 285, 1950. (61) **King, H., Shummacker, H. B., Jr.:** Surgery, **43,** 680, 1958. (62) **Kleckner, M. S., Jr., Kark, R. M., Baker, C. A., Chapman, A. Z., Kaplan, C.,** and **Moore, T. J.:** J. Am. Med. Assn., **57,** 1471, 1955. (63) **Klemperer, P.:** Arch. Path., **8,** 353, 1928. (64) **Knisely, M. H., Harding, F., Debacker, H.:** Science, **125,** 1023, 1957. (65) **Koop, C. E.,** and **Roddy, S. R.:** Ann. Surg., **147,** 17, 1958.

(66) **Large, A. M., Johnston, C. G.,** and **Preshaw, D. E.:** Ibid., **135,** 22, 1952. (67) **Lazzari, J. H.,** and **Rack, F. J.:** A.M.A. Arch. Surg., **62,** 295, 1951. (68) **Leffman,**

H., and **Payne, J. T.**: Am. Surgeon, **21**, 488, 1955. (**69**) **Linton, R. R.**, and **Warren, R.**: Surgery, **33**, 243, 1953. (**70**) **Linton, R. R.**, and **Ellis, D. S.**: J. Am. Med. Assn., **160**, 1017, 1956. (**71**) **Linton, R. R.**: New England J. Med., **238**, 723, 1948. (**72**) **Linton, R. R., Jones, C. M.**, and **Volweiler, W.**: Surg. Clin. N. America, **27**, 162, 1947. (**73**) **Linton, R. R.**: Ann. Surg., **140**, 555. 1954. (**74**) **Longmire, W. P., Jr., Mulder, D. G., Mahoney, P. S.**, and **Mellinkoff, S. W.**: Ann. Surg., **147**, 881, 1958. (**75**) **Lyons, C.**, and **Patton, T. B.**: Surgery, **39**, 540, 1956. (**76**) **Madden, J. L.**: Surg., Gynec. & Obst., **96**, 594, 1953. (**77**) Idem: Rev. Gastroenterol., **20**, 300, 1953. (**78**) **Madding, G. F., Smith, W. L.**, and **Hershberger, L. R.**: J. Am. Med. Assn., **156**, 593, 1954. (**79**) **Mann, F. C., Fishback, F. C., Gay, J. G.**, and **Green, G. F.**: Arch. Path., **12**, 787, 1931. (**80**) **Manning, R. T.**, and **Delp, M.**: New England J. Med., **258**, 55, 1958. (**81**) **Mayo, W. J.**: Ann. Surg., **80**, 419. 1924. (**82**) **McDermott, W. V., Jr., Adams, R. D., Riddel A. G.**: Ann. Surg., **140**, 539, 1954. (**83**) **McDermott, W. V., Jr.**, and **Adams, R. D.**: J. Clin. Invest., **33**, 1, 1954. (**84**) **McFadzean, A. J. S.**, and **Cook, J.**: Lancet, **1**, 615, 1953. (**85**) **McIndoe, A. H.**: Arch. Path., **5**, 23, 1928. (**86**) **Meyer, A.**: Med. Rec., **63**, 806, 1903. (**87**) **Moersch, H. J.**: J. Am. Med. Assn., **135**, 754, 1947. (**88**) **Moschcowitz, E.**: Am. J. Med., **17**, 1, 1954. (**89**) **Moyer, J. H., Ford, R. V.**, and **Spurr, C. L.**: Proc. Soc. Exper. Biol. & Med., **95**, 529, 1957. (**90**) **Mulligan, L. V.**: Soc. Clin. Surg., April, 1958.

(**91**) **Nachlas, N. M.**: New England J. Med., **252**, 720, 1955. (**92**) **Najarian, J. S.**, and **Harper, H. A.**: Am. J. Med., **21**, 832, 1956.

(**93**) **Ogilvie, H.**: Surgery, **34**, 768, 1953. (**94**) **Osler, W.**: J. Anat. & Physiol., **13**, 291, 1878–1879.

(**95**) **Palmer, E. D.**, and **Jahnke, E. J., Jr.**: Am. J. Trop. Med. & Hyg., **3**, 139, 1954. (**96**) **Palmer, E. D.**, and **Brick, I. B.**: New England J. Med., **248**, 1057, 1953. (**97**) **Patek, A. J., Jr., Post, J., Ratnoff, O. D., Mankin, H.**, and **Hillman, R. W.**: J. Am. Med. Assn., **138**, 543, 1948. (**98**) **Pattison, A. C.**: A.M.A. Arch. Surg., **72**, 886, 1956. (**99**) **Patton, T. B.**, and **Johnston, C. G.**: Arch. Surg., **59**, 502. 1949. (**100**) **Patton, T. B.**: Am. Surgeon, **23**, 932, 1957. (**101**) **Patton, T. B.**, and **Lyons, C.**: J. Soc. Internat. Chir. (Brux), in press. (**102**) **Patton, T. B.**: Unpublished data. (**103**) **Patton, T. B., Johnston, C. G., Lyons, C.**, and **Jordan, P., Jr.**: To be published. (**104**) **Patton, T. B., Lyons, C.**, and **Lombardo, C. R.**: Ann. Surg., **143**, 588, 1956. (**105**) **Patton, T. B.**: To be published. (**106**) **Payne, M. A.**, and **Child, C. G. III**: Monographs In Med., (**W. B. Bean**). Baltimore: The Williams & Wilkins Co., p. 132, 1952. (**107**) **Pemberton, J. DeJ.**, and **Kiernan, P.**: S. Clin. N. America, **25**, 880, 1945. (**108**) **Phemister, D. B.**, and **Humphreys, E. M.**: Tr. Am. Surg. Assn., **65**, 17, 1947. (**109**) **Preble, R. B.**: Am. J. Med. Sci., **119**, 263, 1900.

(**110**) **Reynolds, J. T.**, and **Southwick, H. W.**: A.M.A. Arch. Surg., **62**, 789, 1951. (**111**) **Reynolds, T. B., Mikkelson, W.**, and **Redeker, A. G.**: J. Am. Med. Assn., **158**, 478, 1955. (**112**) **Rienhoff, W. F., Jr.**, and **Woods, A. C.**: J. Am. Med. Assn., **158**, 687, 1953. (**113**) **Rosenstein, P.**: Arch. klin. Chir., **98**, 1082, 1912. (**114**) **Rousselot, R. M.**: Surgery, **31**, 403, 1952. (**115**) **Rowntree, L. G., Zimmermann, E. F., Todd, M. H.**, and **Ajac, J.**: J. Am. Med. Assn., **135**, 630, 1957. (**116**) Iidem: Proc. Staff Meet., Mayo Clin., **4**, 263, 1929.

(**117**) **Samuel, E.**: Brit. J. Radiol., **21**, 519, 1948. (**118**) **Schalm, L. H., Bax, H. R.**, and **Mansens, B. J.**: Gastroenterology, **31**, 131, 1956. (**119**) **Sengstaken, R. W.**, and **Blakemore, A. H.**: Ann. Surg., **131**, 781, 1950. (**120**) **Shumacker, H. B., Jr.**, and **King, H.**: A.M.A. Arch. Surg., **65**, 499, 1952. (**121**) **Smookler, B. H.**: Gastroenterology, **31**, 581, 1956. (**122**) **Smythe, C. McC.**, and **Brody, N. B.**: J. Am. Med. Assn., **156**, 31, 1957. (**123**) **Soborov, V.**: Ibid., **158**, 118, 1955. (**124**) **Som, M. L.**, and **Garlock, J. H.**: Ibid., **135**, 628, 1947.

(**125**) **Talma, S.**: Berlin klin. Wchnschr., **35**, 883, 1898. (**126**) **Tansini, I.**: (Translation) Ann. Surg., **36**, 964, 1903. (**127**) **Taylor, F. W.**: Ann. Surg., **140**, 652, 1954. (**128**) **Tocantins, L. M.**: J. Am. Med. Assn., **136**, 616, 1948.

(**129**) **Vidal, E.**: Presse Med., **11**, 747, 1903. (**130**) Idem: Rev. Chir. Paris, **42**, 118, 1910. (**131**) **Vossschulte, K.**: Lyon Chir., **53**, 519, 1957.

(**132**) **Walker, R. M.**: Lancet, **1**, 57, 1957. (**133**) **Walshe, J. M.**: Ibid., **1**, 1075, 1953. (**134**) **Welch, C. S., Kiley, J. E., Reeve, T. S., Goodrich, E. O.**, and **Welch, H. F.**:

New England J. Med., **254**, 493, 1956. (**135**) **Welch, C. S.**: New England J. Med., **255**, 677, 1956. (**136**) **Westphal, K.**: Deutsche med. Wchnschr., **56**, 1135, 1930. (**137**) **Whipple, A. O.**: Ann. Surg., **122**, 449, 1945. (**138**) **Wilcox, A. Y., Jr., Bovill, E. G.,** and **Olivetti, R. G.**: Gastroenterology, **21**, 375, 1952. (**139**) **Womack, N. A.**: Operative Technique (Cole). New York: Appleton-Century-Crofts, Inc., 1956. (**140**) **Zamcheck, N., Chalmers, T. C., Ritvo, M.,** and **Osborne, M. P.**: J. Am. Med. Assn., **148**, 504, 1952. (**141**) **Zieve, L., Hill, E., Nesbitts, S.,** and **Zieve, B.**: Gastroenterology, **25**, 495, 1953.

SUMMARIO IN INTERLINGUA

(See page 204 for original article)

Toxicitate Acute E Tractamento De Intoxication Per Crotalo Adamentee

1. Le injection de veneno de crotalo adamantee per via intramuscular es sequite per le production immediate de effectos local e systemic. Le effectos local al sito del injection o in su vicinitate include marcate grados de edema (apparentemente etiam marcate grados de dolor), sequite per ruptura del pelle, digestion de musculo skeletic, e necrose. Le effectos systemic es confinate a un lethargia general, salivation, diarrhea sanguinose, e morte in coma.

2. Le toxicitate acute (intramuscular) del veneno crystallin (20 a 25% del peso original) varia considerabilemente in differente species. Le *approximative doses letal*, in mg per kg de peso corporee, es le sequente: can, capra, e rheso, 0,64 (2,8); conilio, 0,94 (4,1); columba e gallina, 1,4 (6,2); porco e porco de India, 3,2 (14,0); mus, 10,7 (47,0); e ratto, 25,0 (110,0). (Le valores inter parentheses indica le doses letal del veneno original.)

3. Un morsura typic de crotalo libera approximativemente 650 mg de veneno. Iste quantitate suffice pro occider circa 4 juvene porcos o 12 canes o 15 rattos o 23 juvene capras o 27 conilios o 46 rhesos o 54 procos de India o 162 columbas o 216 gallinas o 325 muses.

4. Le injection intravenose de hydrocortisona (Hydro-Cortef) in canes a periodos de 2 e 4 horas, respectivemente, post le injection intramuscular de duo doses letal approximative (1,28 mg per kg) de veneno crystallin de crotalo adamantee augmentava le numero del canes supervivente ab le valor de controlo de 17% usque a 65% e 75%, respectivemente. Sin le beneficio de cortisona le canes moriva intra circa 18 horas. Le canes que moriva in despecto del administration de cortisona superviveva circa 3 dies. Super le base de iste datos, un can recipiente duo doses letal approximative de veneno e tractate subsequentemente con Hydro-Cortef ha un probabilitate de pauco plus que 50% de superviver. Le administration de cortisona non influentiava visibilemente le local effectos proteolytic o septic o le processo del resanation. Le effecto benefic de cortisona non es comprendite al tempore presente.

OPHTHALMOLOGY

UNDER THE CHARGE OF

WILLIAM L. BENEDICT, M.D.

AND

HENRY P. WAGENER, M.D.
ROCHESTER, MINNESOTA

SOME RECENT STUDIES ON EALES' DISEASE

By HENRY P. WAGENER, M.D.

IN a recent report of his clinical study of nontraumatic intraocular hemorrhage, Gupta[13] stated that 33 of 100 cases were thought to be instances of Eales' disease. In a review in the August, 1935, issue of this Journal, I[49] discussed the problem of recurrent hemorrhages into the retina and vitreous of young adults and noted that most authorities considered Eales' disease to be a manifestation of tuberculous phlebitis and periphlebitis. Focal infections and rather vague endocrine disturbances were suggested by some as the cause of the vascular lesions responsible for the bleeding. In the February, 1940, issue of the Journal, I[50] noted that, impressed by the difficulty of demonstrating the presence of tuberculosis in other parts of the bodies of individuals with recurrent intraocular hemorrhage, Marchesani[31] had suggested that the venous lesions in the retina were part of a generalized systemic thromboangiitis obliterans. After reviewing the statements of a number of authors, some favoring and others opposing Marchesani's views, I reached the following conclusions:

"In summary, it might be said that in the vast majority of the cases, at least, the basic local lesion underlying recurrent hemorrhagic extravasations into the vitreous is a diseased condition in the walls of the retinal vessels, predominantly or primarily in most, if not all instances, in the veins. The distinction between a primarily perivenous and a primarily venous or arterial lesion may be an important one from the etiologic standpoint. An attempt should be made to differentiate these lesions ophthalmoscopically where the vitreous is sufficiently clear to allow careful study of the retinal vessels. A certain number of the cases, particularly of those of perivenous type, may be due to tuberculosis, either primary in the retina or secondary to a hidden or latent focus of tuberculosis in the choroid. In perhaps a larger number of cases in which tuberculosis cannot be demonstrated elsewhere in the body, there may be a primary nonspecific inflammatory or degenerative lesion of the vessel walls. This may be the retinal counterpart of Buerger's disease and may be confined to the retinal vessels or at times may be associated with similar lesions in other parts of the body."

Subsequent experience has made it evident that the occurrence of recurrent intraocular hemorrhages in association with the more usual manifesta-

tions of Buerger's disease in the extremities is sufficiently rare to suggest that the presence of the two lesions in a given individual is coincidental rather than indicative of a common exciting cause. It may well be true, as stated by Doden and Adams[4], that it is possible for thromboangiitis obliterans to involve the retinal vessels and lead to hemorrhage in the retina and vitreous, but that thromboangiitis obliterans is not the cause of the typical retinal periphlebitis of Eales' disease.

EALES' DISEASE AND TUBERCULOSIS. In 1954, Elliot[7] presented a study of 31 cases of Eales' disease. Evidence of active or healed pulmonary tuberculosis was present in 9 cases. The skin tuberculin test was positive in 30 cases and doubtful in 1. Ultimate vision was better in the cases without associated pulmonary tuberculosis; it was good (20/20 to 20/50) in 21 of 34 involved eyes (62%). Final vision of 20/20 to 20/50 was attained in only 4 of 12 involved eyes of 8 patients with pulmonary involvement (33%). The ninth patient in this group came to necropsy, 6 months after the onset of bleeding from the peripheral retinal veins, as a result of caseous tuberculosis of the lungs, of the peribronchial lymph nodes, of the heart and of the pericardium.

Histologic examination of an eye removed at necropsy showed recent hemorrhage and new-formed vessels in the vitreous, glial tissue proliferation in the retina and extending into the vitreous and infiltration of the retina with macrophages. But there was little evidence of inflammatory reaction in the retina around the vessels. Some of the vessels were surrounded by a few lymphocytes and some of the smaller vessels in the periphery showed hyaline thickening of their walls without occlusion of the lumens. Elliot[7] concluded that there was no true inflammatory periphlebitis and that the pathologic changes in the retinal vessels in this early stage were compatible with an allergic basis for the disease.

Two eyes were removed in the late stages of the process because of secondary glaucoma. Peripheral anterior synechiae were present and the iris and ciliary body were infiltrated with lymphocytes and plasma cells. The retinal vessels were surrounded in many areas by cuffs of lymphocytes and the lumens of some of the vessels were obliterated by proliferation of the endothelium. The pathologic lesions were nonspecific in type and not characteristic of tuberculosis.

In summarizing the results of his studies, Elliot[7] stated that the clinical histories and findings in the 31 cases "were so similar that the disease may be considered a clinical entity and not a manifestation of many diseased conditions." He suggested that the condition occurs "in individuals who have been previously sensitized to tuberculoprotein, and the hemorrhage and exudation are a local reaction in a hypersensitive vessel wall."

Franceschetti[10] expressed the opinion that the greater number of cases of Eales' disease are of tuberculous etiology, but it is possible that some cases may be due to a different cause. Kimura, Carriker and Hogan[27] noted that tuberculosis, thromboangiitis obliterans, focal infection and a congenital abnormality of the retinal vessels had all been advanced as possible causes of Eales' disease. They stated that "Of the conditions considered most likely during recent years, only tuberculosis has maintained its position." In their opinion, there is "reasonable proof that tuberculous infections play some part in the causation of retinal vasculitis with vitreous hemorrhages. . . . we believe that the uveal tract or retina

somehow becomes sensitized to tuberculoprotein; later ingestion or administration of a similar protein, regardless of its source, may lead to an inflammatory reaction."

Kimura, Carriker and Hogan[27] defined retinal vasculitis with intraocular hemorrhage as a series of related entities which affect the eyes of young persons, principally males. They classified their cases into 3 types: (1) primary retinal vasculitis, in which the initial lesions involve the peripheral retinal veins in a large percentage of cases, but occasionally the larger veins, in the form of phlebitis and periphlebitis with more or less destruction and necrosis and at times with rupture and extensive bleeding; (2) secondary retinal vasculitis, in which the primary focus is in the ciliary body in the form of a cyclitis with retrograde extension into the retina; and (3) postchoroiditic retinal vasculitis, in which retinal edema and inflammation are secondary to choroiditis.

Eighteen eyes in which the clinical diagnosis of Eales' disease or retinal periphlebitis had been made were examined histopathologically by Kimura and his co-workers[27]. Twelve were found to be instances of primary retinal vasculitis; perivascular lymphocytic infiltration was noted in 8 eyes and granulomatous inflammation of the peripheral retinal veins in 4. The retinal vascular lesions were thought to be secondary in 6 eyes, in 4 of them secondary to granulomatous chorioretinitis. The lesions were not characteristically tuberculous and acid-fast bacilli were not found.

OCCURRENCE AND CHARACTERISTICS OF SICKLE-CELL DISEASE. Quite recently, sickle-cell disease has been added to the possible causes of Eales' disease. According to Hannon[15], it was in 1910 that Herrick[20] described the first case of sickle-cell anemia in man; however, it was not until 1937 that abnormalities of the retinal vessels were first described in the literature by Harden[16] and not until 1952 that definitely pathologic lesions were first reported by Edington and Sarkies[6].

Singer[42] stated, in 1951, that sickle-cell disease is an hereditary syndrome which is manifested either by the sickle-cell trait (sicklemia) of which there are no clinical symptoms, or by sickle-cell anemia, a serious and incapacitating disease. He noted that 8% of the 15,000,000 Negroes in the United States harbor the sickle-cell trait, and that 34,000 to 180,000 of this 1,200,000 have sickle-cell anemia. Assuming that, as generally supposed, sickling of erythrocytes is confined to the Negro race, the cases of Eales' disease which might be based on this etiology would necessarily be strictly limited. However, a few cases of sickle-cell anemia in members of the white race have been reported, and, as noted by Jelliffe[23], it is possible that the sickle-cell trait may occur not uncommonly in non-Negro groups of the population. This author stated that a focus of sickle-cell anemia has been found in Greece and that a definite percentage of the trait has been found among Jewish children from Yemen. Haden and Evans[14] reported sickle-cell anemia in 2 sisters born of Sicilian parents and without history or physical findings suggesting an admixture of Negro blood. Ogden[35] observed 2 cases of active sickle-cell anemia and 7 of the sickling trait in two families, 1 Spanish and 1 German. However, he said that sickling is found in the Negro race only and that, when it is seen in an individual of another race, it indicates admixture of Negro blood in the immediate or remote ancestry. And Chernoff[1] stated: "The limitation of hemoglobin S to persons of Negro blood seems so definite that some in-

vestigators have stated emphatically that the presence of sickling is undeniable proof of Negro ancestry. Occasional reports of sickle-cell disease in Caucasians almost invariably come from areas where admixture with Negro blood is quite likely. In the few reports in which such an admixture seems more remote, adequate family studies have not been carried out to exclude this possibility. Extensive studies by Lehmann[39] and others suggest that the sickling tendency may have arisen as a mutation in the inhabitants of Southern Arabia or in the Veddoid inhabitants of Southern India and have been transported to Africa and subsequently to the Mediterranean area and the Americas through invasion, the use of African mercenaries and the slave trade. Isolated foci of the sickle-cell trait in such areas as central Greece could well have arisen as a result of spontaneous mutations. Nevertheless, it would be difficult to exclude the possibility that this genetic defect was introduced into these regions by miscegenation with African natives known to have visited the lands along the Mediterranean Sea over two thousand years ago."

Pauling, Itano, Singer and Wells[37] noted that tests *in vivo* had demonstrated that between 30 and 60% of the erythrocytes in the venous circulation of sickle-cell anemic individuals are sickled normally, compared to less than 1% of those in the venous circulation of sicklemic individuals. Sickle-cell erythrocytes in which the hemoglobin is combined with oxygen or with carbon monoxide have the biconcave disk contour and are indistinguishable from normal erythrocytes. They are termed promeniscocytes. If the oxygen or carbon monoxide is removed, transforming the hemoglobin to the uncombined state, the promeniscocytes undergo sickling. The addition of oxygen or carbon monoxide to the cells reverses this phenomenon. They thought that distortion of the erythrocyte might result from a change in the surface configuration of the globin molecule in the sickle cell. These investigators demonstrated for the first time that there is a significant difference between the electrophoretic mobility of hemoglobin derived from the erythrocytes of normal individuals and that of hemoglobin derived from the erythrocytes of sickle-cell anemic individuals. They showed also that the hemoglobin derived from the erythrocytes of individuals with sicklemia appears to be a mixture of normal and sickle-cell anemic hemoglobins in roughly equal proportions. In a later publication, Singer[42] gave the percentages of the different types of hemoglobin as normal 55% to 77%, S 45% to 23% and fetal none in sicklemics; and normal none, S 76% to 98% and fetal 24% to 2% in sickle-cell anemics.

In discussing the pathology of sickle-cell disease, Murphy and Shapiro[33] wrote: "Sickling is a property inherent in the red blood cell and not dependent on external factors. It is precipitated *in vivo* or experimentally by alterations in the ratio of combined to dissociated hemoglobin within the cell. In the body this alteration depends on the oxygen tension of the plasma. In the presence of high oxygen tension most of the hemoglobin exists in the combined form as oxyhemoglobin. In this state the red blood cells tend to remain entirely normal in shape and behavior. As the oxygen tension is lowered and the hemoglobin contained in the red blood cell correspondingly dissociated to the reduced form, the cells begin one by one to sickle, until finally (experimentally) 100% of them can be made to assume abnormal form." As noted previously, Pauling and his associates[37] suggested later that

it is a change in the surface configuration of the abnormal globin molecule that results in the change in shape of the red blood cell.

Murphy and Shapiro[33] went on to say that, when sickling occurs, the cell loses its almost jelly-like flexibility and appears as fixed and rigid as a crystal of ice. The sickled cell is the wrong shape and is too rigid and unyielding to get through terminal capillaries. As the sickled cells increase in number, they eventually impact the capillaries, cause stasis in the blood flow and initiate thrombosis. These authors considered the fundamental pathologic lesion of sickle-cell disease to be mechanical obstruction of capillaries and vascular thromboses. Singer[42] contended, however, that blocking of flow in small vessels and thrombosis do not explain all the features of sickle-cell anemia. There is a shortened life span of the erythrocyte in sickle-cell anemia, he stated. Also the hemolytic tendency of the anemia cell is caused by an intracorpuscular defect which is absent in the trait cell. Henry and Chapman[19] suggested that the stasis, thrombosis and hemorrhage resulting from the impaction of sickled cells in the capillaries would cause a further decrease in the oxygen supply to the local vasculature with ensuing endarteritis and infarction of the area. And Goodman, von Sallmann and Holland[12] noted that, in addition to the rigidity and abnormal shape of the sickled cells, there is a definite increase in the viscosity of the sickled blood which is attributed to the enmeshing and interlocking of the sickled erythrocytes. The viscous conglomerates which develop in the small vessels may lead to obstruction and infarction without the formation of true thrombi.

The Retinal Lesions of Sickle-Cell Anemia. In 1930, Cook[3] reported a case of sickle-cell anemia in a Negro boy, aged 7. Death resulted from a subarachnoid hemorrhage, confirmed at necropsy. Two fresh hemorrhages were present in the right retina; but these quite probably were secondary to the subarachnoid hemorrhage rather than related directly to the sickle-cell anemia. In 1937, Harden[16] described moderate tortuosity of the retinal arteries and great dilatation and tortuosity of the retinal veins in 2 brothers with sickle-cell anemia. The fundi were otherwise normal and Harden[16] thought that the retinal vessels were congenitally abnormal. In 1942, Klinefelter[28] stated that, of 12 patients with cardiac lesions associated with sickle-cell anemia, 7 showed moderate to marked dilatation and tortuosity of the retinal veins. This finding could not be correlated with the other cardiovascular anomalies, with the ulcers on the legs or with the duration of the anemia. In 1944, Ray and Cecil[39] described the observation of very tortuous retinal veins in a 15-year-old Negro girl who had infectious mononucleosis complicated by sickle-cell anemia. In 1950, in a clinical study of 54 cases of sickle-cell anemia, Henderson[18] noted the presence of retinal hemorrhage in 1 case; he gave no details of this finding, however. And it was not until 1952 that a report appeared in which a definite connection between sickle-cell anemia and abnormal findings in the retina seemed to be established.

Edington and Sarkies[6], in 1952, reported the finding of retinal microaneurysms in each of 2 patients with sickle-cell anemia. A small hemorrhage was seen in the retina near 1 of the microaneurysms in 1 patient. The vision of 1 eye of the other patient was reduced to light perception by a dense hemorrhage in the vitreous. Both cases "gave the rheumatic-like history with the presence of numerous target

cells and signs of increased haemolysis in the peripheral blood. Sickling of the red blood cells was present, and, in addition, radiological evidence of bone changes" in the skull described as characteristic of sickle-cell anemia. The authors stated: "The blockage of small blood vessels by sickled erythrocytes with stasis and subsequent thrombosis is a common pathological lesion in sickle-cell anemias and might be the aetiological factor concerned in the production of the microaneurysms reported in these 2 cases."

In 1954, Henry and Chapman[19] reported on the retinal lesions observed in 29 patients with sickle-cell disease. Hemorrhages were found in the retinas of 3 of 19 patients showing the sickle-cell trait. In one of these cases, the hemorrhage in the retina was associated with chorioretinal atrophy and hemorrhage into the vitreous; in another case fluffy white patches were present in the retina in addition to the hemorrhages. An area of apparent proliferating retinopathy was noted in a fourth patient with the sickle-cell trait. Hemorrhages in the retina and vitreous were noted in 2 patients with sickle-cell anemia; proliferating retinopathy was noted in both of these patients and chorioretinal atrophy in one. Areas of chorioretinal atrophy were found in 2 other cases of sickle-cell anemia. In a fifth case, the retinal vascular tree was dilated and tortuous and three areas of glial proliferation were present in 1 retina. The authors thought that the areas of glial proliferation in the retina and those of chorioretinal atrophy resulted from arterial infarcts in the retina and choroid.

Sub-types of Sickle-Cell Disease. In 1953, Smith and Conley[43] described a method of filter paper electrophoresis which had enabled them to separate various types of abnormal hemoglobins by a relatively simple and clinically applicable technique. They designated normal hemoglobin as hemoglobin A, fetal hemoglobin as hemoglobin F, sickle-cell hemoglobin as hemoglobin S and 2 other abnormal hemoglobins as hemoglobin C and hemoglobin D. According to this terminology, hemoglobin S–S is found in sickle-cell anemia, hemoglobin S–A in sickle-cell trait, hemoglobin S–C in sickle-cell-hemoglobin C disease, and hemoglobin C–A in hemoglobin C trait. Among 500 white persons there were no instances of S, C–S or C–A hemoglobins. Among 500 Negroes there were 5 instances of hemoglobin S–S, 36 of hemoglobin S–A, 1 of hemoglobin S–C and 9 of hemoglobin C–A. According to Smith and Conley[43], patients with sickle-cell-hemoglobin C disease usually have only mild anemia and no jaundice, but they may develop hemolytic episodes with jaundice and profound anemia. They may have pain in the extremities. Two of their 7 patients had gross unilateral hematuria.

In the same year, Neel, Kaplan and Zuelzer[34] stated: "The presence of hemoglobin C is readily demonstrated by electrophoretic studies of hemoglobin suspensions, and may be suspected hematologically in the presence of abnormal numbers of target cells. The tendency to form hemoglobin C appears to depend on a single mendelian factor inherited as a dominant. . . . The combination of this factor with the genetic factor responsible for the sickling phenomenon results in a hemolytic anemia of varying degrees of severity." These authors recognized 4 genetically distinct subtypes of the hemolytic anemias associated with, and presumably due to the sickling phenomenon. They listed in the order of frequency of occurrence sickle-cell anemia (due to homozygosity of the gene responsible for the sickling phenomenon), sickle-cell-hemoglobin C

disease (due to the presence in the same individual of the gene for hemoglobin C and the sickling gene), sickle-cell-thalassemia disease and sickle-cell-hemoglobin D disease. The same authors[25] noted that the clinical course of sickle-cell-hemoglobin C disease is mild and that specific complaints are few. There is little interference with normal activity, growth or development. There is mild chronic anemia with erythrocyte sickling and target cells. The hemolytic disturbance is clearly due to an inherited intrinsic erythrocyte defect. They added that the combined presence of hemoglobin C and normal hemoglobin constitutes the hemoglobin C trait. In this condition, the hemoglobin, the erythrocyte count and the reticulocyte count are within normal limits and there is no sickling of the red cells, but numerous target cells are present in the blood.

Hays and Engle[17] called attention to the fact that homozygous hemoglobin C, all the hemoglobin being of the C type, gives rise to a mild hemolytic anemia and an increase of target cells in the peripheral blood. They presented a study of the family of an individual whose sickle-cell-hemoglobin C disease was asymptomatic. They stated: "Study of this family shows that the patient transmits either the gene for hemoglobin C or the gene for sickle hemoglobin to his offspring, who also inherit a gene for normal hemoglobin from their mother. The offspring therefore show the asymptomatic traits for hemoglobin C and sickling. This indicates that the genes for hemoglobin C and sickle hemoglobin may occupy the same locus on the chromosome, a phenomenon which has been called allelomorphism, or nearly the same locus which has been called close linkage. Either property would make it impossible for an individual with sickle cell-hemoglobin C disease when mated to a normal individual to have offspring with both abnormal hemoglobins. Such mechanisms would, however, insure the inheritance by each offspring of one or the other of the genes for abnormal hemoglobin."

In 1954, Smith and Conley[44] presented a study of the clinical features of the genetic variants of sickle-cell disease. They listed 15 cases of sickle-cell anemia, 16 cases of sickle-cell-hemoglobin C disease, 4 of sickle-cell-thalassemia disease, 3 of them in persons of the white race, 2 cases of unclassified sicklemia and 1 of sickle-cell-congenital hemolytic jaundice. They stated that they had observed tortuosity of the retinal veins in all but one of the sickle-cell anemia group, in 2 of the sickle-cell-hemoglobin C group and in one of the sickle-cell-thalassemia group. Hemorrhage had occurred into the vitreous in 3 patients in the sickle-cell-hemoglobin C group. The hemorrhage in the vitreous in one of these cases was associated with a uveitis presumed to be tuberculous. The hemorrhage in the first eye of another of the cases followed severe trauma to the eye; but a hemorrhage into the vitreous of the second eye of this individual occurred spontaneously 10 years later. In the third case, the hemorrhage into the vitreous of one eye was associated with a group of aneurysmal dilatations in the vessels in the macular region; similar findings were observed in the other eye at a later date. Unilateral optic atrophy was present in one patient of the sickle-cell-hemoglobin C group, but it was presumed to be of syphilitic origin. Smith and Conley[44] commented, "While it has not been definitely established that these retinal lesions were the result of the underlying blood disorder, their frequency and peculiar nature suggest this possibility in at least some instances."

It is of interest to note that, in 1953, Rudd, Evans and Peeney[40] had reported their observation of recurrent hemorrhage and exudation in the retina with exudation into the vitreous of a pure West African Negro, aged 22, whose blood showed sickling of the erythrocytes and also the characteristics of thalassemia minor. (Thalassemia major is regarded as a manifestation of the homozygous form of thalassemia hemoglobin and thalassemia minor is regarded as a manifestation of the heterozygous form of this hemoglobin.)

In commenting on this case at a later date, Goodman, von Sallmann and Holland[12] noted that the hematologic findings would be consistent also with sickle-cell-hemoglobin C disease and that hemoglobin electrophoresis would have been necessary to establish the correct diagnosis. There were many target cells in the blood smear and the high incidence of hemoglobin C disease in West Africa would favor the diagnosis of sickle-cell-hemoglobin C disease.

Retinal Lesions in Sickle-Cell-Hemoglobin C Disease. In 1956, Hannon[15] noted that various genetically determined abnormalities of hemoglobin, in addition to sickle-cell hemoglobin, had been discovered by means of hemoglobin electrophoresis. Some of these abnormal hemoglobins "when coexisting with sickle-cell hemoglobin, gave rise to diseases previously mistaken for sickle-cell anemia or sickle-cell trait." He added, "All the previous reports of ocular pathologic processes associated with sickle-cell disease were presented prior to knowledge that these variants existed and there is no correlation between the clinical picture and the exact hematologic diagnosis." With these facts in mind, Hannon[15] reviewed the records of 140 cases admitted to the Johns Hopkins Hospital with diagnoses of sickle-cell anemia, sickle-cell trait or atypical sickle-cell disease and obtained hemoglobin electrophoretic studies on a number of these patients. On the basis of these studies, 20 patients were placed in the category of sickle-cell-hemoglobin C disease and 5 in that of sickle-cell-thalassemia disease. Admitting that a great majority of the remaining 115 cases had not yet been reclassified on the basis of hemoglobin electrophoresis, Hannon[15] considered 53 to be instances of sickle-cell anemia and 62 to belong to the sickle-cell trait group. Twenty-five (47%) of the 53 cases of sickle-cell anemia showed dilated and tortuous retinal veins as compared with only 1 of the 62 cases of sickle-cell trait. Retinopathy or hemorrhages into the vitreous were not observed in any of the 115 cases. All of the 5 cases of sickle-cell-thalassemia disease had normal eyes. Seven of the 20 patients with sickle-cell-hemoglobin C disease had hemorrhage into the vitreous or retinopathy, or both. The ocular pathology seemed to be related unequivocally to sickle-cell-hemoglobin C disease in 5 of these 7 cases. The vision of one eye of 4 of the 5 patients was reduced to light perception by the presence of massive hemorrhage in the vitreous. In the eyes in which the fundi were visible, Hannon[15] said, "The earliest vascular abnormality observed was the appearance of a neovascular-like, anastomotic network of fine vessels, apparently in relation to venules, in the peripheral temporal quadrant. Initially the findings appear to be localized to the peripheral temporal quadrants, but as the disease progresses changes are seen in other quadrants as well. The most important finding, and the presumed site of occurrence of ultimate hemorrhaging, is the appearance of twisted, corkscrewlike venules arranged in a multiple arborizing

fashion, with terminal dilatations appearing to extend into the vitreous. Multiple occlusions of terminal venules and arterioles are also seen. One patient showed salmon-pink to whitish exudative plaques in the peripheral retinal quadrants in association with involved vessels."

On the basis of hemoglobin electrophoretic studies, Kennedy and Cope[26] separated 20 cases of sickle-cell disease into 17 of sickle-cell trait, 2 of sickle-cell anemia and 1 of sickle-cell-hemoglobin C disease. The patient with sickle-cell-hemoglobin C disease gave a history of numerous episodes of blurred vision, more in the right eye. The vision of the right eye was reduced to light perception by a massive hemorrhage in the vitreous. In the fundus of the left eye were 1 large and 4 smaller areas of chorioretinal atrophy from 2 of which glial tissue proliferations projected into the vitreous. The retinal veins were dilated and tortuous but the retina was normal otherwise. One of the patients with sickle-cell trait gave a history of previous hemorrhage into the vitreous of the right eye but showed at the time of examination only an area of healed chorioretinitis above and temporal to the right optic disk. Another patient with sickle-cell trait showed marked tortuosity of all the vessels coming off the right optic disk. This abnormal tortuosity extended for only a short distance from the disk margins, however. One of the patients with sickle-cell anemia, a 34-year-old man of Greek origin, had in the periphery of the left fundus 2 areas of hyperpigmentation and glial tissue excess. Kennedy and Cope[26] thought that the intraocular lesions in the cases of sickle-cell trait and of sickle-cell anemia might or might not have been the result of the abnormal hemoglobins. However, the patient with sickle-cell-hemoglobin C disease, they said, "had such a unique picture in his visible fundus that we feel it was the result of his abnormal hemoglobin."

Goodman, von Sallmann and Holland[12] reported the ocular changes present in 4 cases of electrophoretically proven sickle-cell-hemoglobin C disease. The intraocular lesions included retinal, preretinal and vitreous hemorrhage, retinitis proliferans, tortuous and anastomosing arterioles and venules either alone or in association with proliferating glial and fibrous tissue masses, multiple saccular and varicose aneurysmal dilatations, arborizing vascular networks, vascular loops projecting into the vitreous, focal constrictions, dilatations, sheathing and obstruction of arterioles and venules and the development of chalk-white vessels owing to changes in intravascular contents. Histologic examination in the enucleated eye of one of these cases revealed a complicated cataract, retinal gliosis blending with a preretinal fibrous membrane, extensive new vessel formation, obliterated vessels, perivenous lymphocytic cuffing and hemorrhages in the retina and in the vitreous. Sickled cells were noted intravascularly and also in the hemorrhagic extravasations.

These authors described also the retinal lesions in a fifth patient, a Negro woman, aged 18, with known sickle-cell disease who developed blurring of vision of the left eye during labor. She was found to have edema of the retina extending from the disk to the macular area, retinal and preretinal hemorrhages, and narrowing, dilatations, focal constrictions and interruptions of the blood columns in arterioles and venules. Later, a large portion of the retinal vascular bed became chalk white in color. During a 3-month period of observation the whiteness partially disappeared. The authors com-

mented, "Though the exact nature of the obstructive vascular process in this patient was uncertain, the focal involvement of vessels in all quadrants suggested multiple lesions due to vasospasm or intravascular obstructions." Hemoglobin electrophoresis and solubility studies demonstrated the presence of sickle-cell hemoglobin and another abnormal hemoglobin of similar electrophoretic mobility, suggesting sickle-cell-hemoglobin D disease. This diagnosis could not be confirmed by familial hemoglobin studies for, though the patient's mother was shown to have the sickle-cell trait, the father was not available for study. As noted by Goodman and his co-workers[12], "Sickle-cell hemoglobin C disease has been found in all the previous reports of retinopathy in electrophoretically studied cases of sickle-cell disease and in four of five patients in the present study." I understand, however, that retinal lesions have been observed recently in some other, as yet unreported, cases of sickle-cell-hemoglobin D disease. Goodman and his associates[12] called attention, in a footnote, to 2 more cases of retinitis proliferans in sickle-cell-hemoglobin C disease which had been observed by Iser[22] and by Simpson[41].

In discussing the mechanism of production of the vascular obstructive lesions in the retina in sickle-cell-hemoglobin C disease, Goodman, von Sallmann and Holland[12] noted that the "retina possesses a high rate of glycolysis, which favors a rapid depletion of oxygen from circulating red blood cells. This may be an important factor in the precipitation or augmentation of sickling within the retinal capillary bed. Furthermore, the presence of an end-arteriole system in the retina predisposes to anoxia and tissue damage once blockage occurs." These authors admitted that venous stasis is probably of considerable importance in accounting for the retinal lesions of sickle-cell disease. But they pointed out that "in the present investigation it was frequently observed that vascular networks and microaneurysms developed distal to obstructed arterioles, as well as venules." They noted also that "Hemorrhage is a serious complication of sickle-cell retinopathy. It is presumably secondary to the vascular changes, since bleeding tendencies due to hematologic abnormalities are not characteristic of sickle-cell disease and they have been specifically ruled out in the 4 patients of this study with intraocular hemorrhage." And they thought that the chalk-white appearance of portions of the retinal vessels which was noted in 2 of their cases was due, not to changes in the vessel walls but to abnormalities in the intraluminal contents, most probably hemolyzed sickled erythrocytes, as suggested by Fine[9]. Fine demonstrated by electron microscopy that the white material produced by hemolysis *in vitro* of normal or sickled erythrocytes consisted of masses of fragmented erythrocyte membranes devoid of hemoglobin. The significance of the sausage-like dilatation of fine conjunctival vessels, the massing of red blood cells in the dilated segments and of saccular microaneurysms of the conjunctival vessels observed in some cases is as yet not determined, according to Goodman and his co-workers[12].

Kabakow, Van Weimokly and Lyons[24] observed closure of the left central retinal artery and, 13 days later, closure of the right central retinal artery of a Negro woman, aged 36, suffering from proved systemic lupus erythematosus, active pulmonary tuberculosis and sickle-cell trait. They thought that the arterial occlusions were associated with the systemic lupus. Goodman, von Sallmann and

Holland[12] commented that the presence of several concomitant disease processes made it impossible to reach a definite conclusion as to the role played by the sickle-cell trait in the development of the retinal arterial occlusions. But, in the light of this report and of the observation by Clifford and Tanaka[2] of retinal microaneurysms and hemorrhage into the vitreous in a 39-year-old Negro man with the sickle-cell trait only, they suggested that the sickle-cell trait may not be a clinically benign carrier state and that it may be incriminated at times in the development of vascular occlusions.

As noted by Goodman, von Sallmann and Holland[12], the correlation of retinal lesions with the different genotypic forms of sickle-cell disease will require careful ophthalmoscopic examinations with particular attention to the peripheral retina and to the recognition of early changes and adequate hematologic investigation including hemoglobin electrophoresis, to identify the exact sub-type of sickle-cell disease. It will be important in the future to carry out special hematologic studies on Negroes and on Caucasians of Mediterranean origin (Italians, Greeks and Turks, for example) in whom the diagnosis of Eales' disease has been made. If a sickling tendency is demonstrated by the standard sodium metabisulfate test, the types of abnormal hemoglobins present should be investigated by filter paper electrophoresis. If such studies are made and if ophthalmoscopic examinations and hemoglobin electrophoretic studies are carried out in all cases of sickle-cell disease, it will be possible to determine the incidence of retinal vascular lesions among individuals with erythrocyte sickling.

TREATMENT OF RECURRENT HEMORRHAGES INTO THE RETINA AND VITREOUS. Medical treatments instituted for the control of recurrent intraocular bleeding have been largely unsatisfactory. Most of them have been based on the probable tuberculous etiology of the underlying retinal vascular lesions. As pointed out by Elliot[7], tuberculin therapy and general hygienic measures have not been uniformly successful in the control of the disease process. In spite of favorable reports by some authors such as Sykowski[45], Kratka[29] and Velicky[47], the results obtained by use of the bactericidal drugs have not been too good. This is not surprising in view of the failure to demonstrate the presence of tubercle bacilli in the retinal lesions. Kimura, Carriker and Hogan[27] stated that antituberculous therapy did not alter the course of the disease in their series of cases and that they considered the indiscriminate use of antituberculous drugs to be not only unnecessary but wrong. Opinions differ on the value of cortisone and corticotropin. Elliot[7] found that these hormones controlled the bleeding in 3 of his cases. Hoffmann[21] reported that he had treated 60 cases of hemorrhage into the vitreous associated with periphlebitis by irradiation with radium or Roentgen ray and that full vision was regained in 42 of 98 eyes with periphlebitis. This type of treatment has not met with general acceptance.

Recently, surgical methods of treatment have been advocated as the most logical method for prevention of recurrence of the bleeding in these cases. Pajtás[36] succeeded in arresting the course of the disease in 6 of 8 cases of tuberculous retinal periphlebitis by the use of perforating electrocoagulation combined with the administration of streptomycin and para-aminosalicylic acid. However, the method generally recommended is the application of surface diathermy to the sclera over the areas of involved retinal veins.

While observing the course of the retinal periphlebitis in the second eye of a young man who had lost the vision of one eye as a result of recurrent hemorrhages into the vitreous, Verhoeff[18] reasoned that nonperforating diathermy applied over involved areas to destroy the inflammatory foci, whether tuberculous or not, and to prevent dissemination from them, would obliterate the vessels from which the hemorrhages arose and would seal down the retina so that it could not be pulled off by the retinitis proliferans. He reported in 1947 that there had been no recurrence of bleeding into the eye for 14 months after the second application of diathermy. Apparently, no further reports on this method of treatment were published during the next 6 years.

Since 1954, a number of authors have reported good results obtained by surface diathermy coagulation of the sclera over the areas of retinal vessel involvement, when these areas are visible. Among these authors are Fanta[8], Vail[46], Payne and Crick[38] and Merz and Hauser[32]. Franceschetti and Forni[11] reported that they had carried out surface diathermy on 13 eyes of 11 patients. Five eyes had been treated for prophylaxis of bleeding as venous lesions were present in the retina but hemorrhage had not occurred as yet. Hemorrhages did not appear in 3 of these eyes during a 4-year period of observation. In one eye, there was an excellent initial result, but a plastic iridocyclitis developed 18 months later. There had been no bleeding in the fifth eye during the 6 months following the operation. In 8 eyes in which there had already been hemorrhage into the vitreous, surface diathermy coagulation was carried out for therapeutic reasons, to prevent recurrence of the bleeding if possible. In 5 of these eyes, there had been no recurrence of bleeding during periods of observation ranging from 1½ to 6 years. Two of the 5 eyes required 2 operations and 1 eye was operated upon 3 times. No follow-up was obtained as to the condition of 2 of the eyes and 1 eye had been operated too recently to determine the ultimate result.

Donders[5] discussed the results obtained in the diathermy treatment of some of the cases of Eales' disease in the Weve Clinic. Good results were obtained in 7 of the 10 patients whom they were able to follow for from 1 to 16 years; 3 of these had required 2 operations. He commented that long-lasting and presumably permanent cure may be expected in many cases. However, in some cases, the operation has unfavorable effects. Extensive hemorrhage developed after the first operation in 1 case and after a second operation in another. Donders[5] thought that, for the time being, the operation should be limited to those cases in which only a few vessels are affected. It is not desirable to intervene in advanced cases with widely extended localization and secondary retinal detachment. He advised that, in general, care should be taken to apply a minimum of diathermic energy and to allow sufficient intervals between individual coagulations to avoid heat injury to neighboring vessels.

Goodman, von Sallmann and Holland[12] noted that there is no specific treatment at present for the hemoglobin disorder underlying sickle-cell retinopathy. Hannon[15] recommended surface diathermy over the involved vessels as employed for the prevention of future hemorrhages in cases with recurrent intraocular bleeding due to other causes. He himself operated on the better eye of each of 2 patients who had lost the vision of one eye

as the result of massive hemorrhage into the vitreous. One of the eyes had been treated too recently to judge the ultimate result of the procedure. But the other eye had shown no new lesions during a 2½-year period of observation and had maintained 20/20 vision. Goodman and his co-workers[12] agreed that this was a logical and conservative approach to the problem of therapy and they noted that one of Hannon's patients who had refused the recommended prophylactic surgery later developed a massive hemorrhage into the vitreous of the second eye so that his vision was reduced to light perception.

Conclusions. To quote from Verhoeff[48], "Recurring retinal hemorrhages in young persons are frequently associated with ophthalmoscopically recognizable periphlebitis. In most cases the patients give skin reactions to tuberculin, and in the cases in which the retina has been examined microscopically, nodular foci of epithelioid cells have been found along the veins. These facts constitute strong evidence that the condition . . . is an entity, that it is caused by tuberculosis and that to it most cases of so-called Eales' disease belong."

There is a trend at present toward elimination of eponyms from medical diagnosis. But, if the term, Eales' disease, is retained, it is suggested that this diagnosis be reserved for those instances of recurrent hemorrhage into the retina and vitreous of young adults in which there are evidences of present or past tuberculosis in the lungs or elsewhere or positive reactions to skin tuberculin tests and in which no other logical cause for the bleeding can be found.

Instances of recurrent intraocular hemorrhage which are part of the symptomatology of known and definitely diagnosable systemic diseases such as diabetes and sickle-cell disease and distinct entities should not be diagnosed Eales' disease, but should be termed retinopathy of diabetes or retinopathy of sickle-cell disease, as the case may be, with recurrent hemorrhage into the retina and vitreous.

Whether or not there is such an entity as thromboangiitis obliterans of the retinal vessels is as yet not definitely determined.

ADDENDUM: Since this review was completed, **E. W. Hook** and **G. R. Cooper** (South. Med. J., **51**, 610, 1958) have reported on the ocular findings in 25 patients with sickle-cell anemia and in 15 patients with sickle-cell-hemoglobin C disease. They found that tortuosity was more common and more pronounced in the retinal veins than in the arterioles, and in the case of sickle-cell anemia than in the cases of sickle-cell-hemoglobin C disease. In one of their patients with sickle-cell-hemoglobin C disease prerential hemorrhages and papilledema developed in association with a subarachnoid hemorrhage. One of their patients with sickle-cell anemia had a questionable quiescent or residual proliferative retinopathy.

REFERENCES

(1) **Chernoff, A. I.**: New England J. Med., **253**, 322, 365, 416, 1955. (2) **Clifford, C.**, and **Tanaka, C.**: Quoted by **Goodman, G., von Sallmann, L.**, and **Holland, M. G.**[12]. (3) **Cook, W. C.**: J. Med., **11**, 541, 1930.
(4) **Doden, W.**, and **Adams, A.**: Klin. Monatsbl. f. Augenheilk., **129**, 305, 1956. (5) **Donders, P. C.**: Ophthalmologica, **132**, 334, 1956.
(6) **Edington, G. M.**, and **Sarkies, J. W. R.**: Tr. Roy. Soc. Trop. Med. & Hyg., **46**, 39, 1952. (7) **Elliot, A. J.**: Tr. Am. Ophthal. Soc., **52**, 811, 1954.
(8) **Fanta, H.**: Wien. klin. Wchnschr., **66**, 809, 1954. (9) **Fine, B.**: Quoted by **Goodman, G., von Sallmann, L.**, and **Holland, M. G.**[12]. (10) **Franceschetti, A.**: Am. J.

Ophthal., **39**, 189, 1955. (**11**) **Franceschetti, A.**, and **Forni, S.**: Acta 17th Concilium Ophthalmologicum (1954), **1**, 215, 1955.
(12) **Goodman, G., von Sallmann, L.**, and **Holland, M. G.**: A.M.A. Arch. Ophthal., **58**, 655, 1957. (**13**) **Gupta, S. P.**: Ophthal. Lit. (Abstract), **11**, 217, 1957.
(14) **Haden, R. L.**, and **Evans, F. D.**: Arch. Int. Med., **60**, 133, 1937. (**15**) **Hannon, J. F.**: Am. J. Ophthal., **42**, 707, 1956. (**16**) **Harden, A. S., Jr.**: Am. J. Dis. Child., **54**, 1045, 1937. (**17**) **Hays, E. F.**, and **Engle, R. L., Jr.**: Ann. Int. Med., **43**, 412, 1955. (**18**) **Henderson, A. B.**: Am. J. Med., **9**, 757, 1950. (**19**) **Henry, M. D.**, and **Chapman, A. Z.**: Am. J. Ophthal., **38**, 204, 1954. (**20**) **Herrick, J. B.**: Quoted by **Hannon, J. F.**[15]. (**21**) **Hoffmann, W.**: Klin. Monatsbl. f. Augenheilk., **126**, 575, 1955.
(22) **Iser, G.**: Quoted by **Goodman, G., von Sallmann, L.**, and **Holland, M. G.**[12].
(23) **Jelliffe, D. B.**: Tr. Roy. Soc. Trop. Med. & Hyg., **46**, 169, 1952.
(24) **Kabakow, B., Van Weimokly, S. S.**, and **Lyons, H. A.**: A.M.A. Arch. Ophthal., **54**, 670, 1955. (**25**) **Kaplan, E., Zuelzer, W. W.**, and **Neel, J. V.**: Blood, **8**, 735, 1953. (**26**) **Kennedy, J. J.**, and **Cope, C. B.**: A.M.A. Arch. Ophthal., **58**, 163, 1957. (**27**) **Kimura, S. J., Carriker, F. R.**, and **Hogan, M. J.**: A.M.A. Arch. Ophthal., **56**, 361, 1956. (**28**) **Klinefelter, H. F.**: Am. J. Med. Sci., **203**, 34, 1942. (**29**) **Kratka, W. H.**: A.M.A. Arch. Ophthal., **54**, 330, 1955.
(30) **Lehmann, H.**: Quoted by **Chernoff, A. I.**[1].
(31) **Marchesani, O.**: Quoted by **Wagener, H. P.**[50]. (**32**) **Merz, E. H.**, and **Hauser, P.**: Am. J. Ophthal., **43**, 882, 1957. (**33**) **Murphy, R. C., Jr.**, and **Shapiro, S.**: Ann. Int. Med., **23**, 376, 1945.
(34) **Neel, J. V., Kaplan, E.**, and **Zuelzer, W. W.**: Blood, **8**, 724, 1953.
(35) **Ogden, M. A.**: Arch. Int. Med., **71**, 164, 1943.
(36) **Pajtás, J.**: Ophthalmologica, **126**, 116, 1953. (**37**) **Pauling, L., Itano, H. A., Singer, S. J.**, and **Wells, I. C.**: Science, **110**, 543, 1949. (**38**) **Payne, I. W.**, and **Crick, R. P.**: Brit. J. Ophthal., **40**, 492, 1956.
(39) **Ray, E. S.**, and **Cecil, R. C.**: South. Med. J., **37**, 543, 1944. (**40**) **Rudd, C., Evans, P. J.**, and **Peeney, A. L. P.**: Brit. J. Ophthal., **37**, 353, 1953.
(41) **Simpson, G. V.**: Quoted by **Goodman, G., von Sallmann, L.**, and **Holland, M. G.**[12]. (**42**) **Singer, K.**: Am. J. Clin. Path., **21**, 858, 1951. (**43**) **Smith, E. W.**, and **Conley, C. L.**: Bull. Johns Hopkins Hosp., **93**, 94, 1953. (**44**) Iidem: Ibid., **94**, 289, 1954. (**45**) **Sykowski, P.**: Am. J. Ophthal., **34**, 889, 1951.
(46) Vail, D.: Year Book of Eye, Ear, Nose and Throat, Chicago: Year Book Publishers, Inc., p. 134, 1955–56. (**47**) **Velicky, J.**: Ophthalmologica, **129**, 111, 1955. (**48**) **Verhoeff, F. H.**: Tr. Am. Ophthal. Soc., **45**, 194, 1947.
(49) **Wagener, H. P.**: Am. J. Med. Sci., **190**, 286, 1935. (**50**) Idem: Ibid., **199**, 296, 1940.

BOOK REVIEWS AND NOTICES

L'Encéphalographie Fractionée. By Giovanni Ruggiero. Pp. 510; 288 figs. containing 843 ills. Paris: Masson et Cie, 1957. Price 13.500 fr.

This monograph is based upon the author's rich experience in fractional air-encephalography collected first at Lindgren's radiologic service at the Serafimer Hospital in Stockholm, later in the author's own service at the Neurosurgical Center of the Hôpital St. Anne in Paris. In the first part of the book, the technique of the fractional air-encephalography, the dynamic mechanisms involved, possible complications are outlined in detail and the material is statistically analyzed. A correct diagnosis in tumors was accomplished in 85.3% of the cases. The second part is devoted to the interpretation of normal ventricles and subarachnoid spaces and to pathologic studies in malformations, space-taking lesions, cerebral atrophy and inflammatory diseases of the brain and the meninges. With its excellent illustrations, this book will be of value not only to neurosurgeons and neuroradiologists but also to neurologists and radiologists in general. E. S.

Fundamentals of Electrocardiography and Vectorcardiography. By Lawrence E. Lamb, M.D., Director of Cardiology and Chief, Department of Internal Medicine, Air University, School of Aviation Medicine, USAF, Randolph Air Force Base, Texas. Pp. 142; 158 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $9.50.

In this beautifully printed book, the author proposes to set forth the basic fundamentals of electrocardiography and vectorcardiography. To do this, he begins with an elementary discussion of the concept of vectors. The difference between an instantaneous resultant vector and the component vectors from which it is derived is clearly explained. The succeeding chapters on the cell as a source of electrical activity, the heart as a source of electrical forces (which is clearly reminiscent of concepts developed by Ashman and Gardberg) and the discussions of volume conductors are hardly adequate even for a primer.

A novel feature following the discussion on electrocardiographic leads and the normal electrocardiogram is a chart which permits rapid approximation of the spatial QRS–T angle. The relation of this angle to the spatial gradient is not discussed.

The author uses a vectorcardiographic system derived from electrodes placed equidistant from the center of the left ventricle determined by roentgenographic examination. The reviewer is not familiar with patterns so derived.

That part devoted to clinical electrocardiography is sketchy and, the reviewer thinks, is at times misleading.

The reviewer thinks that this text is not adequate for a student who desires to learn how to make use of either electrocardiography or vectorcardiography. Unfortunately, no references are given to guide him to more detailed information. L. S.

International Symposium on Hemophilia and Hemophilioid Diseases. Edited by Kenneth M. Brinkhous, M.D., Professor of Pathology, University of North Carolina. Pp. 265; 73 ills., 6 in color (1 plate). Chapel Hill: University of North Carolina Press, 1957. Price, $7.50.

The proceedings of an international symposium on Hemophilia and the Hemophilioid Diseases, which was held in New York in 1956, are recorded in this volume. The material is presented in 7 major sections headed, respectively, as follows: The Clotting Defect in Hemophilia; The Hemophilioid States; Diagnosis of Hemophilia; Management of Hemorrhage in Hemophilia and Related Diseases; Hemophilic Arthropathy; and Psychiatric and Socioeconomic Aspects of Hemophilia.

There is much authoritative information in this book. It is recommended to anyone interested in a summary of the current status of hemophilia and related diseases. C. Z.

Atlas d'Anatomie Stéréotaxique. By J. Talairach, M. David, P. Tournoux, H. Corredor and T. Kvasina. Pp. 294; 91 plates and 99 figs. Paris: Masson et Cie, 1957. Price, 10.000 fr.

After introduction of the stereotaxic method in the surgery of the brain by American authors (1947), Talairach and David were the first European neurosurgeons who tried

this method; since 1949 they carried out systematic anatomic studies. The present atlas is the result of these studies. It shows the coordinates of various subcortical areas in relation to a line connecting the anterior and posterior commissures. For roentgenologic visualization a distance of 4.2 meters between Roentgen-ray tube and film is used in an attempt to avoid distortion by use of "parallel" roentgenograms. This goal, of course, can only be approximately attained. Such a teleradiography necessitates a large radiologic room, long irradiation; the difficulty of centering also should not be overlooked. The illustrations are excellently reproduced; however, readers not very familiar with the intimate histology of the various subcortical nuclei may experience some difficulties in identifying them, since a large part of the figures fail to show detailed lettering. More information about the individual variations would also be desirable. Despite these difficulties, neuroradiologists and neurosurgeons will find much valuable information in this atlas. E. S.

Symposium on Diseases and Surgery of the Lens. Edited by George M. Haik, M.D., Professor of Ophthalmology, Louisiana State University School of Medicine, and Elizabeth M. McFetridge, M.D. Pp. 238; 230 ills. St. Louis: The C. V. Mosby Co., 1957. Price, $10.50.

This is a well organized book based on the Transactions of the New Orlean's Academy of Ophthalmology, 1956.

The round-table discussions are centered on the formal presentations made by six well known panelists. The book covers lens development, anatomy, pathology, usual techniques of removal, and complications. It can easily be used as a reference because of its carefully organized index of subjects.

There is a lively and interesting 38-page round-table discussion that covers many controversial subjects in which all of the panel members freely discuss their personal methods and comment on those of the other members.

From subjects, such as types and number of sutures used to close corneal sections, one can see how his technique varies or compares with others.

It was interesting to note that no one keeps patients with uncomplicated cataracts flat in bed any more, and furthermore that the patient's stay in the hospital is governed more by the medico-legal aspects of the state in which he is operated upon than any feeling that it would be less proper to send him home on the fourth than the fourteenth day.

This is a worthwhile and easily readable book. The illustrations deserve special mention. L. H.

Clinical Heart Disease. By Samuel A. Levine, M.D., Clinical Professor of Medicine, Harvard Medical School. 5th ed. Pp. 673; 216 ills. Philadelphia: W. B. Saunders Co., 1958. Price, $9.50.

Proper interpretation of results of gadgetry applied to clinical medicine depends mainly upon sound clinical knowledge. No amount of statistical manipulation, regardless of degree of probability obtained, makes erroneous observations valid. Yet, observations at the bed-side are at once simple and complex. They are simple to see but difficult to recognize or as Auenbrugger said, "one cannot see until one has learned to see." Dr. Levine presents, in this the fifth edition of his book, the knowledge he has gained from a lifetime devoted to learning the heart. The presentation is succinct, with proper emphasis on common disorders. It is also rich in personal experiences, without being cluttered by extensive references to others, for this is his work. Here may be found the bed-side method for the recognition of systolic murmurs and for the determination of their nature and significance, tricks for evaluation of the origin of chest pain, rationale and advantages of chair rest, old and new therapy for cardiac disorders, and a host of unanswered questions for meditation. Master clinician though he be, modest he remains, for the chapters on congenital heart disease and electrocardiography are written by Alexander Nadas and Harold Levine, both capable physicians. All physicians, in practice or not and regardless of interest, will find in this book a rewarding experience which can lead only to a better understanding of the heart and a wiser approach to the person with heart disease. J. Z.

Introduction to Biostatistics. By Huldah Bancroft, Ph.D. Professor of Biostatistics. Tulane University of Louisiana School of Medicine. Pp. 210; 37 ills. New York: A Hoeber-Harper Book, 1957. Price, $5.75.

This volume deals mainly with statistical methods which are appropriate for large samples. Frequency distributions, tabulation, graphing, use of centering constants and measures of variation are treated in the introductory chapters. The chi-square test, *t* tests,

vital statistics, bioassay and the Reed-Muench method are also discussed.

The book is written in simple, nontechnical terms and is particularly recommended for medical students and physicians who have had little training in mathematics. C. Z.

MORPHOLOGIE UND PHYSIOLOGIE DES NERVENSYSTEMS. BY PROF. DR. PAUL GLEES, OXFORD. Pp. 445; 149 ills. Stuttgart: Georg Thieme. 1957 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $13.80.

THE author, well known for his morphological studies, attempts to integrate morphologic and physiological aspects of the nervous system. While the morphologic chapters are excellent, the physiologic parts are rather spotty. Detailed chapters deal with the auditory and visual systems, while hardly more than a few lines are devoted to the vestibular system; there is a large chapter on the hypothalamus as the center of vital functions while such an important center as the respiratory center is hardly mentioned. The author deals in a peculiar way with the literature; for example, the classic experiments of Karplus and Kreidl on the hypothalamus are omitted; in discussing stereotactic lesions of the thalamic nuclei in man he fails to mention the original work, but quotes a paper by Monnier and Lauer which deals with the diencephalon of the rabbit; the original stereotactic operations on the basal ganglia are neglected, but subsequent Spanish, Polish and Japanese authors are quoted. The author believes that Magoun has "discovered" the reticular system (page 312), while the preceding work of Flechsig, Kohnstamm, Wallenberg, the demonstration of the role of this system in decerebrate rigidity (Spiegel) are ignored. The illustrations, a large part of which are original, are excellently reproduced.

E. S.

LA PSYCHANALYSE ET LES ULCÈRES GASTRO-DUODENAUX. BY ANGEL GARMA, President of the Argentine Psychoanalytic Society and Professor of the University of La Plata. Pp. 178. Paris: Presses Universitaires de France, 1957. Price, Fr. 700.

DR. GARMA presents the case histories of patients suffering with gastro-duodenal ulcers. The verbal productions of these patients obtained during psychoanalysis is presented and interpreted.

The author presents his theory of the psychological disturbances in ulcer. The internalized bad mother acts aggressively against the patient already orally regressed. The patient persists in an unconscious attitude of infantile submission to parental prohibitions. When unconscious psychic representations of the bad mother are reactivated, it is as though a bad conscience attacks the alimentary tract. The eating patterns of the patients are affected, acting adversely on the digestive system.

The author is convinced that treatment directed at the etiology of the ulcer must be aimed at modifying the unconscious psyche of the patient. M. B.

RHYTHMUSSTÖRUNGEN DES HERZENS. BY KONRAD SPANG, Medical Departments, Heidelberg and Katharinen Hospital, Stuttgart. Contributors, W. DOERR, Department of Pathology, Kiel, and W. TRAUTWEIN, Department of Physiology, Heidelberg. Pp. 548, text, pp. 111, atlas; 109 ills., text, 228 ills. atlas. 2034 references. Stuttgart: Georg Thieme Verlag, 1957 (Intercontinental Medical Book Corp., New York, U.S. Agents). Price, $35.25.

THIRTY years have elapsed since Wenckebach and Winterberg published their monumental work on the irregular heart action. This volume is a worthy successor.

The chapters on the morphology and pathology of the conduction system by Doerr and on the physiology of the cardiac irregularities by Trautwein are monographs in themselves and provide the student in the field with basic information.

The first part of the main section represents a very complete description of all known disturbances of the rhythm of the heart, with many schematic graphs facilitating their understanding (only experts know how complicated the matter is). Continuous reference is made to the associated clinical symptoms, signs and problems. The second part goes into the etiology and clinical significance of disturbed cardiac rhythm, to mention: infectious-toxic myocardial disease, endocrine and metabolic diseases, pregnancy, allergy, myocardial infarction and fibrosis, relations to the central and peripheral vegetative nervous system, carotid sinus reflex, effect of posture, effort, psychic forces, occurrence in congenital c-v anomalies, trauma and electric shock, venous and arterial embolism, deleterious effects of drugs, disturbances in conjunction with angiocardiography, cardiac catheterization, hypothermia, intracardiac operation. The

third part deals with therapeutic aspects; it first gives a veritable pharmacology and physiology of cardiac drugs and then proceeds to the treatment of the disturbances of rhythm, sinustachy- and bradycardia, supraventricular paroxysmal tachycardia, atrial flutter and fibrillation, premature beats, ventricular tachycardia and fibrillation, disturbances of conduction, Morgagni-Adams-Stokes seizures, and carotid sinus syndrome.

Throughout the text there are clinical cases described and the appropriate graphs appear in the atlas portion.

The illustrations are of superior quality.

The reviewer is unaware of the existence of such a complete and integrated presentation elsewhere. H. R.

SURGERY IN WORLD WAR II: OPHTHALMOLOGY AND OTOLARYNGOLOGY. Edited by COLONEL JOHN BOYD COATES, JR., MC, Editor in Chief. Pp. 605; 136 ills. and 2 color plates. Washington: U.S. Government Printing Office, 1957. Price, $5.00.

THE administrative and clinical aspects of ophthalmology and otolaryngology in the Army Medical Department in World War II have been brought together in one volume of which more than two-thirds is devoted to ophthalmology. While the record of administrative experiences may lack appeal to the civilian physician nevertheless this information is of inestimable value for organization and planning in future conflicts. Appropriate emphasis on the effects and management of traumatic lesions is balanced by detailed consideration of the incidence, relative importance and significance of the clinical entities encountered in the military practice of ophthalmology and otolaryngology.

The record of introduction of new techniques during the war is fascinating, including as it does, the development of the acrylic eye, the establishment of an efficient and practical program for the rehabilitation of blinded eye casualties, the management of selected cases of psychogenic deafness by narcosynthesis, and the organization of the first integrated aural rehabilitation program. This volume is an important source of information concerning the military aspects of ophthalmology and otolaryngology. H. S.

EISEN, KUPFER UND EIWEISS AM BEISPIEL DER LEBERKRANKHEITEN. Mit besonderer Berücksichtigung der Haemochromatose und der hepatocerebralen Degeneration. By PROV.-DOZ. DR. J. LANGE, Bonn. Pp. 89; 30 ills. Stuttgart: Georg Thieme Verlag, 1958 (Intercontinental Medical Book Corporation, New York, U.S. Agents). Price, $3.20.

THIS monograph, written in German, is a masterful work summarizing the studies by the author on the normal metabolism of iron and copper and in various diseases of the liver and biliary tract, both acute and chronic. The latest experimental data concerning the absorption, transport, deposition and excretion of these metals and the roles played by their complex protein combinations concerned with these processes are clearly described.

Of especial interest is the section dealing with hemochromatosis and hepato-lenticular degeneration (Wilson's disease). Here, the clinical, biochemical and pathological findings are well correlated with the therapeutic approaches in these diseases. Many diagrams are included which beautifully demonstrate the factual data.

The Bibliography is excellent and includes 428 references.

The fact that this work is in German will unfortunately limit its usefulness. It is nevertheless highly recommended to those interested in liver disease. D. B.

Mother and Child. A Primer of First Relationships. By D. W. WINNICOTT, M.D., Physician, Paddington Green Children's Hospital, London, England; also President of the British Psychoanalytic Society. Pp. 210. New York: Basic Books, Inc., 1957. Price, $3.50.

DOCTOR WINNICOTT, a British pediatrician and psychoanalyst, presents a theme best expressed by the author's words to mothers who read the book. "I am trying to describe various aspects of the things you do naturally in order that you may be able to recognize what you do and in order that you may be able to get the feeling of your natural capacity."

The first half of the book deals warmly and clearly with facets of the mother-child relationship such as feeding, weaning, crying and toilet-training. The remainder discusses problems arising in family relationships, adoption, being an only child or twin, lying and stealing.

Although apparently primarily intended for mothers, this could be valuable reading for physicians, social workers and nurses. M. B.

Psychobiology. By ADOLF MEYER, M.D., Late Henry Phipps Professor of Psychiatry, Johns Hopkins University. Compiled and translated from Dr. Meyer's manuscripts and edited by EUNICE E. WINTERS AND

ANNA MAE BOWERS. Pp. 257; 4 ills. Springfield, Ill.: Charles C Thomas, 1957. Price, $6.50.

THIS first Thomas William Salmon Memorial lecture has been published posthumously more than 25 years after it was delivered.

The first lecture defines Dr. Meyer's psychobiological integrative concept of psychiatry. His approach is holistic and illustrates an integrative evolution between the humanities and the natural sciences.

The second lecture deals with pathology. The concept of reaction emphasizing the dynamics of psychosis, is considered a valuable contribution to American psychiatry.

The third lecture is a contribution to therapy. The fundamental responsibility of the physician to the patient is emphasized. Psychobiologically oriented psychiatry bases its treatment on the principle that normal activities can be encouraged thus causing less normal tendencies to recede.

M. B.

Psychology, Religion and Human Need: A Guide for Ministers, Physicians, Teachers and Social Workers. BY W. L. CARRINGTON, M.D. Pp. 315. Great Neck, N.Y.: Channel Press, 1957. Price, $3.75.

THIS book, developed from lectures to students of the Anglican Theological College of Melbourne, is the product of the author's experience as physician, psychiatrist, and lay pastor. Dr. Carrington discusses some of the principles of psychology and psychiatry, particularly the technique of counseling, as a method of understanding the problems of the individual. This approach, however, is limited, according to the author. He states, "This psychological approach to clarification and interpretation is generally essential, but it will be incomplete unless it is deepened by an attempt to relate the whole situation, thus clarified, to the Christian Conception of life. . ." The essential setting for this further clarification and interpretation will have been established already through the counseling relationship of empathy progressively experienced by the client from the beginning." Therefore, Dr. Carrington proposes the training of the pastoral counselor in order to augment "scientific healing," and discusses Christian doctrine at some length to demonstrate how it would serve such a purpose.

M. B.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Published Monthly. Illustrated.

Subscription price: 1 year $10.00; 2 years $18.00.

(One year subscription to Canada, South and Central America and Spain, $10.50; all other countries $12.00)

All foreign subscriptions payable in advance in United States dollars.

Business Correspondence: Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, Pa.

NOTICE AND INSTRUCTIONS TO CONTRIBUTORS

MANUSCRIPTS intended for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES, and correspondence should be sent to the Editor:

DR. RICHARD A. KERN, Temple University School of Medicine, Philadelphia 40, Pa.

Articles are accepted for publication in THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES exclusively, except in the case of subsequent publication in Society proceedings.

MANUSCRIPTS should be typewritten on one side only, of good quality paper and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle.

ILLUSTRATIONS accompanying articles should be numbered and have typed captions bearing corresponding numbers. For identification they should also have the author's name written on the margin or back. Line drawings and charts should be prepared with black India ink. Special arrangements can be made for printing color plates, elaborate tables or an excessive number of illustrations.

REFERENCES should be numbered and at the end of the articles arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

RETURN POSTAGE should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

100 REPRINTS will be supplied gratis. Covers will be omitted on all articles. Orders of additional reprints will be supplied in multiples of 100. An order form showing cost of reprints is sent with proof. Individual reprints can usually be obtained by writing directly to the author.